EXHIBIT 36

RETIN-A®

(tretinoin)

Cream Gel Liquid
For Topical Use Only

Prescribing Information

Description: RETIN-A Gel, Cream, and Liquid, containing tretinoin are used for the topical treatment of acne vulgaris. RETIN-A Gel contains tretinoin (retinoic acid, vitamin A acid) in either of two strengths, 0.025% or 0.01% by weight, in a gel vehicle of butyl alcohol, hydroxypropyl cellulose and alcohol (denatured with *tert*-butylated hydroxytoluene, and brucine sulfate) 90% w/w. RETIN-A (tretinoin) Cream contains tretinoin in either of three strengths, 0.1%, 0.05%, or 0.025% by weight, in a hydrophilic cream vehicle of stearic acid, isopropyl myristate, polyoxyl 40 stearate, stearyl alcohol, xanthan gum, sorbic acid, butylated hydroxytoluene, and purified water. RETIN-A Liquid contains tretinoin 0.05% by weight, polyethylene glycol 400, butylated hydroxytoluene and alcohol (denatured with *tert*-butyl alcohol and brucine sulfate) 55%. Chemically, tretinoin is *all-trans*-retinoic acid and has the following structure:

Leave space for structure.

Clinical Pharmacology: Although the exact mode of action of tretinoin is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedo formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones.

Indications and Usage: RETIN-A is indicated for topical application in the treatment of acne vulgaris. The safety and efficacy of the long-term use of this product in the treatment of other disorders have not been established.

Contraindications: Use of the product should be discontinued if hypersensitivity to any of the ingredients is noted.

Warnings: GELS ARE FLAMMABLE. AVOID FIRE, FLAME OR SMOKING DURING USE. Keep out of reach of children. Keep tube tightly closed. Do not expose to heat or store at temperatures above 120°F (49°C).

Precautions: *General:* If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during the use of RETIN-A, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.

RETIN-A (tretinoin) acne treatment should be kept away from the eyes, the mouth, angles of the nose, and mucous membranes. Topical use may induce severe local erythema and peeling at the site of application. If the degree of local irritation warrants, patients should be directed to use the medication less frequently, discontinue use temporarily, or discontinue use altogether. Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.

Drug Interactions: Concomitant topical medication, medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime should be used with caution because of possible interaction with tretinoin. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid with RETIN-A. It also is advisable to "rest" a patient's skin until the effects of such preparations subside before use of RETIN-A is begun.

Carcinogenesis, Mutagenesis, Impairment to Fertility: In a 91-week dermal study in which CD-1 mice were administered 0.017% and 0.035% formulations of tretinoin, cutaneous squamous cell carcinomas and papillomas in the treatment area were observed in some female mice. A dose-related incidence of liver tumors in male mice was observed at those same doses. The maximum systemic doses associated with the administered 0.017% and 0.035% formulations are 0.5 and 1.0 mg/kg/day, respectively. These doses are two and four times the maximum human systemic dose, when adjusted for total body surface area. The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose (MTD) of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice. There was no evidence of carcinogenic potential when 0.025 mg/kg/day of tretinoin was administered topically to mice (0.1 times the maximum human systemic dose, adjusted for total body surface area). For purposes of comparisons of the animal exposure to systemic human exposure, the maximum human systemic dose is defined as 1 gram of 0.1% RETIN-A applied daily to a 50 kg person (0.02 mg tretinoin/kg body weight).

Studies in hairless albino mice suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light form a solar simulator. This effect has been confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources.

The mutagenic potential of tretinoin was evaluated in the Ames assay and in the *in vivo* mouse micronucleus assay, both of which were negative.

In dermal Segment I fertility studies of another tretinoin formulation in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (4 times the maximum human systemic dose adjusted for total body surface area), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day (2 times the maximum human systemic dose adjusted for total body surface area) and above were observed. A dermal Segment III study with RETIN-A has not been performed in any species. In oral Segment I and Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (16 times the human topical does adjusted for total body surface area).

Pregnancy: Teratogenic effects. Pregnancy Category C. Oral tretinoin has been shown to be teratogenic in rats, mice, hamsters, and subhuman primates. It was teratogenic and fetotoxic in Wistar rats when given orally or topically in doses greater than 1 mg/kg/day (8 times the maximum human systemic dose adjusted for total body surface area). However, variations in teratogenic doses among various strains of rats have been reported. In the cynomolgus monkey, which metabolically is closer to humans for tretinoin than the other species examined, fetal malformations were reported at doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (83 times the maximum human systemic does adjusted for total body surface area), although increased skeletal variations were observed at all doses. A dose-related increase in embryolethality and abortion was reported. Similar results have also been reported in pigtail macaques.

Topical tretinoin in animal teratogenicity tests has generated equivocal results. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (8 times the maximum human systemic dose adjusted for total body surface area). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day was topically applied.

There are other reports in New Zealand White rabbits administered doses of greater than 0.2 mg/kg/day (3.3 times the maximum human systemic dose adjusted for total body surface area) of an increased incidence of domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species.

In contrast, several well-controlled animals studies have shown that dermally applied tretinoin may be fetoxic, but not overly teratogenic in rats and rabbits at doses of 1.0 and 0.5 mg/kg/day, respectively (8 times the maximum human systemic does adjusted for total body surface area in both species).

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty human cases of temporally associated congenital malformations have been reported during two decades of clinical use of RETIN-A. Although no definite pattern of teratogenicity and no causal association has been established from these cases, five of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

Nonteratogenic effects:
Topical tretinoin has been shown to be fetotoxic in rabbits when administered 0.5 mg/kg/day (8 times the maximum human systemic dose adjusted for total body surface area). Oral tretinoin has been shown to be fetotoxic, resulting in skeletal variations and increased intrauterine death in rats when administered 2.5 mg/kg/day (20 times the maximum human systemic dose adjusted for total body surface area).

There are, however, no adequate and well-controlled studies in pregnant women. Tretinoin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when RETIN-A is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 12 have not been established.

Geriatric Use: Safety and effectiveness in a geriatric population have not been established. Clinical studies of RETIN-A did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients.

Adverse Reactions: The skin of certain sensitive individuals may become excessively red, edematous, blistered, or crusted. If these effects occur, the medication should either be discontinued until the integrity of the skin is restored, or the medication should be adjusted to a level the patient can tolerate. True contact allergy to topical tretinoin is rarely encountered. Temporary hyper- or hypopigmentation has been reported with repeated application of RETIN-A. Some individuals have been reported to have heightened susceptibility to sunlight while under treatment with RETIN-A. To date, all adverse effects of RETIN-A have been reversible upon discontinuance of therapy (see Dosage and Administration Section).

Overdosage: If medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. Oral ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

Dosage and Administration: RETIN-A Gel, Cream or Liquid should be applied once a day, before retiring, to the skin where acne lesions appear, using enough to cover the entire affected area lightly. Liquid: the liquid may be applied using a fingertip, gauze pad, or cotton swab. If gauze or cotton is employed, care should be taken not to oversaturate it, to the extent that the liquid would run into areas where treatment is not intended. Gel: Excessive application results in "pilling" of the gel, which minimizes the likelihood of over application by the patient.

Application may cause a transitory feeling of warmth or slight stinging. In cases where it has been necessary to temporarily discontinue therapy or to reduce the frequency of application, therapy may be resumed or frequency of application increased when the patients become able to tolerate the treatment.

Alteration of vehicle, drug concentration, or dose frequency should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance.

During the early weeks of therapy, an *apparent* exacerbation of inflammatory lesions may occur. This is due to the action of the medication on deep, previously unseen lesions and should not be considered a reason to discontinue therapy.

Therapeutic results should be noticed after two to three weeks but more than six weeks of therapy may be required before definite beneficial effects are seen.

Once the acne lesions have responded satisfactorily, it may be possible to maintain the improvement with less frequent applications, or other dosage forms.

Patients treated with RETIN-A (tretinoin) acne treatment may use cosmetics, but the area to be treated should be cleansed thoroughly before the medication is applied. **(See Precautions)**

How Supplied:

RETIN-A (tretinoin) is supplied as:

RETIN-A Cream

NDC Code	RETIN-A Strength/Form	RETIN-A Qty.
0062-0165-01	0.025% Cream	20g
0062-0165-02	0.025% Cream	45g
0062-0175-12	0.05% Cream	20g
0062-0175-13	0.05% Cream	45g
0062-0275-23	0.1% Cream	20g
0062-0275-01	0.1% Cream	45g

RETIN-A Gel

NDC Code	RETIN-A Strength/Form	RETIN-A Qty.
0062-0575-44	0.01% Gel	15g
0062-0575-46	0.01% Gel	45g
0062-0475-42	0.025% Gel	15g
0062-0475-45	0.025% Gel	45g

RETIN-A Liquid

NDC Code	RETIN-A Strength/Form	RETIN-A Qty.
0062-0075-07	0.05% Liquid	28 mL

Storage Conditions: RETIN-A Liquid, 0.05%, and RETIN-A Gel, 0.025% and 0.01%: store below 86°F. RETIN-A Cream, 0.1%, 0.05%, and 0.025%: store below 80°F.

Ortho Dermatological
Division of Ortho-McNeil Pharmaceutical, Inc.
Skillman, New Jersey 08558

(new logo)

RETIN-A®

(tretinoin)

PATIENT INSTRUCTIONS

Acne Treatment

IMPORTANT

Read Directions Carefully Before Using

Cream Gel Liquid

For Topical Use Only

THIS LEAFLET TELLS YOU ABOUT RETIN-A (TRETINOIN) ACNE TREATMENT AS PRESCRIBED BY YOUR PHYSICIAN. THIS PRODUCT IS TO BE USED ONLY ACCORDING TO YOUR DOCTOR'S INSTRUCTIONS, AND IT SHOULD NOT BE APPLIED TO OTHER AREAS OF THE BODY OR TO OTHER GROWTHS OR LESIONS. THE LONG-TERM SAFETY AND EFFECTIVENESS OF THIS PRODUCT IN OTHER DISORDERS HAVE NOT BEEN EVALUATED. IF YOU HAVE ANY QUESTIONS, BE SURE TO ASK YOUR DOCTOR.

WARNINGS

RETIN- A GELS ARE FLAMMABLE. AVOID FIRE, FLAME OR SMOKING DURING USE. Keep out of reach of children. Keep tube tightly closed. Do not expose to heat or store at temperatures above 120°F (49°C).

PRECAUTIONS

The effects of the sun on your skin. As you know, overexposure to natural sunlight or the artificial sunlight of a sunlamp can cause sunburn. Overexposure to the sun over many years may cause premature aging of the skin and even skin cancer. The chance of these effects occurring will vary depending on skin type, the climate and the care taken to avoid overexposure to the sun. Therapy with RETIN-A may make your skin more susceptible to sunburn and other adverse effects of the sun, so unprotected exposure to natural or artificial sunlight should be minimized.

Laboratory findings. When laboratory mice are exposed to artificial sunlight, they often develop skin tumors. These sunlight-induced tumors may appear more quickly and in greater number if the mouse is also topically treated with the active ingredient in RETIN-A, tretinoin. In some studies, under different conditions, however, when mice treated with tretinoin were exposed to artificial sunlight, the incidence and rate of development of skin tumors was reduced. There is no evidence to date that tretinoin alone will cause the development of skin tumors in either laboratory animals or humans. However, investigations in this area are continuing.

Use caution in the sun. When outside, even on hazy days, areas treated with RETIN-A should be protected. An effective sunscreen should be used any time you are outside (consult your physician for a recommendation of an SPF level which will provide you with the necessary high level of protection). For extended sun exposure, protective clothing, like a hat, should be worn. Do not use artificial sunlamps while you are using RETIN-A. If you do become sunburned, stop your therapy with RETIN-A until your skin has recovered.

Avoid excessive exposure to wind or cold. Extremes of climate tend to dry or burn normal skin. Skin treated with RETIN-A may be more vulnerable to these extremes. Your physician can recommend ways to manage your acne treatment under such conditions.

Possible problems. The skin of certain sensitive individuals may become excessively red, swollen, blistered or crusted. If you are experiencing severe or persistent irritation, discontinues the use of RETIN-A and consult your physician.

There have been reports that, in some patients, areas treated with RETIN-A developed a temporary increase or decrease in the amount of skin pigment (color) present. The pigment in these areas returned to normal either when the skin was allowed to adjust to RETIN-A or therapy was discontinued.

Use other medication only on your physician's advice. Only your physician knows which other medications may be helpful during treatment and will recommend them to you if necessary. Follow the physician's instructions carefully. In addition, you should avoid preparations that may dry or irritate your skin. These preparations may include certain astringents, toiletries containing alcohol, spices or lime, or certain medicated soaps, shampoos and hair permanent solutions. Do not allow anyone else to use this medication.

Do not use other medications with RETIN-A which are not recommended by your doctor. The medications you have used in the past might cause unnecessary redness or peeling.

If you are pregnant, think you are pregnant or are nursing an infant: No studies have been conducted in humans to establish the safety of RETIN-A in pregnant women. If you are pregnant, think you are pregnant, or are nursing a baby, consult your physician before using the medication.

AND WHILE YOU'RE ON RETIN-A THERAPY

Use a mild, non-medicated soap. Avoid frequent washings and harsh scrubbing. Acne isn't caused by dirt, so no matter how hard you scrub, you can't wash it away. Washing too frequently or scrubbing too roughly may at times actually make your acne worse. Wash your skin gently with a mild bland soap. (Two or three times a day should be sufficient). Pat skin dry with a towel. Let the face dry 20-30 minutes before applying RETIN-A. Remember,

excessive irritation such as rubbing, too much washing, use of other medications not suggested by your physician, etc., may worsen your acne.

HOW TO USE RETIN-A (TRETINOIN)

To get the best results with RETIN-A therapy, it is necessary to use it properly. Forget about the instructions given for other products and the advice of friends. Just stick to the special plan your doctor has laid out for you and be patient. Remember, when RETIN-A is *used properly*, many users see improvement by 12 weeks. AGAIN, FOLLOW INSTRUCTIONS - BE PATIENT - DON'T START AND STOP THERAPY ON YOUR OWN - IF YOU HAVE QUESTIONS, ASK YOU DOCTOR.

To help you use the medication correctly, keep these simple instructions in mind.

(Insert picture)

- Apply RETIN-A once daily before bedtime, or as directed by your physician. Your physician may advise, especially if your skin is sensitive, that you start your therapy by applying RETIN-A every other night. First, wash with a mild soap and dry your skin gently. WAIT 20 TO 30 MINUTES BEFORE APPLYING MEDICATION; it is important for skin to be completely dry in order to minimize possible irritation.
- It is better not to use more than the amount suggested by your physician or to apply more frequently than instructed. Too much may irritate the skin, waste medication and won't give faster or better results.
- Keep the medication away from the corners of the nose, mouth, eyes and open wounds. *Spread away from these areas when applying.*
- *RETIN-A Cream:* Squeeze about a half inch or less of medication onto the fingertip. While that should be enough for your whole face, after you have some experience with the medication you may find you need slightly more or less to do the job. The medication should become invisible almost immediately. If it is still visible, you are using too much. Cover the affected area lightly with RETIN-A (tretinoin cream) Cream by first dabbing it on your forehead, chin and both cheeks, then spreading it over the entire affected area. Smooth gently into the skin.
- *RETIN-A Gel:* Squeeze about a half inch or less of medication onto the fingertip. While that should be enough for your whole face, after you have some experience with the medication you may find you need slightly more or less to do the job. The medication should become invisible almost immediately. If it is still visible, or if dry flaking occurs from the gel **within a minute or so**, you are using too much. Cover the affected area lightly with RETIN-A (tretinoin gel) Gel by first dabbing it on your forehead, chin and both cheeks, then spreading it over the entire affected are. Smooth gently into the skin.

- *RETIN-A Liquid.* RETIN-A (tretinoin liquid) Liquid may be applied to the skin where acne lesions appear, spreading the medication over the entire affected area, using a fingertip, gauze pad, or cotton swab. If gauze or cotton is employed, care should be taken not to oversaturate it to the extent that the liquid would run into area where treatment is not intended (such as corners of the mouth, eyes, and nose).
- It is recommended that you apply a moisturizer or a moisturizer with sunscreen that will not aggravate your acne (noncomedogenic) every morning after you wash.

WHAT TO EXPECT WITH YOUR NEW TREATMENT

RETIN-A works deep inside your skin and this takes time. You cannot make RETIN-A work any faster by applying more than one dose each day, but an excess amount of RETIN-A may irritate your skin. Be patient.

There may be some discomfort or peeling during the early days of treatment. Some patients also notice that their skin begins to take on a blush.

These reactions do not happen to everyone. If they do, it is just your skin adjusting to RETIN-A and this usually subsides within two to four weeks. These reactions can usually be minimized by following instructions carefully. Should the effects become excessively troublesome, consult your doctor.

BY THREE TO SIX WEEKS, some patients notice an appearance of new blemishes (papules and pustules). At this stage it is *important to continue* using RETIN-A.

If RETIN-A is going to have a beneficial effect for you, you should notice a continued improvement in your appearance after 6 to 12 weeks of therapy. Don't be discouraged if you see no immediate improvement. Don't stop treatment at the first signs of improvement.

Once your acne is under control you should continue regular application of RETIN-A until your physician instructs otherwise.

IF YOU HAVE QUESTIONS

All questions of a medical nature should be taken up with your doctor. For more information about RETIN-A (tretinoin), call our toll-free number: 800-426-7762. Call between 9:00 a.m. and 3:00 p.m. Eastern Time, Monday through Friday.

Ortho Dermatological
Division of Ortho-McNeil Pharmaceutical, Inc.
Skillman, New Jersey 08558

(new logo)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Markham Luke
6/10/02 11:40:52 AM
Acting for Dr. Jonathan Wilkin, Division Director, DDDDP

EXHIBIT 37

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 16-921 S021/022/025
NDA 17-340 S032/033/036
NDA 17-522 S022/023/026
NDA 17-579 S018/020/023
NDA 17-955 S019/020/023
NDA 19-049 S007/008/011

Johnson & Johnson Consumer Companies, Inc.
Attention: Stephanie Davis
Manager, Regulatory Affairs
199 Grandview Avenue
Skillman, New Jersey 08558-9418

Dear Ms. Davis:

Please refer to the following supplemental new drug applications dated December 1, 1995 and received December 4, 1995:

NDA 16-921/S021, NDA 17-340/S032, NDA 17-522/S022, NDA 17-579/S018, NDA 17-955/S019 and NDA 19-049/S007; supplemental drug applications dated January 7, 1997 and received January 8, 1997:

NDA 16-921/S022, NDA 17-340/S033, NDA 17-522/S023, NDA 17-579/S020, NDA 17-955/S020 and NDA 19049/S008, and supplemental drug applications dated August 10, 2000 and received August 11, 2000:

NDA 16-921/S025, NDA 17-340/S036, NDA 17-522/S026, NDA 17-579/S023, NDA 17-955/S023 and NDA 19-049/S011 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Retin-A (tretinoin) Liquid, Retin-A (tretinoin) Cream, 0.1%, Retin-A (tretinoin) Cream, 0.05%, Retin-A (tretinoin) Gel, 0.025%, Retin-A (tretinoin) Gel, 0.01%, and Retin-A (tretinoin) Cream, 0.025%.

We also acknowledge receipt of correspondence dated May 3 and 14, and July 27, 2001; and February 12, and June 3 and 4, 2002, to NDA 16-921/S022, NDA 17-340/S033, NDA 17-522/S023, NDA 17579/S019, NDA 17955/S020, and NDA 19-049/S008.

In addition, we acknowledge receipt of correspondence dated June 3 and 4, 2002 to NDA 16-921/S021, NDA 17-340/S032, NDA 17-522/S022, NDA 17-579/S018, NDA 17-955/S019 and NDA 19-049/S007.

These supplemental new drug applications provide for a combined labeling for all Retin-A products, with the addition of a **WARNINGS** section in the package insert, as well as on the carton and container, that Retin-A Gels are flammable; and the addition of **"Pediatric Use"** and **"Geriatric Use"** subsection to the **PRECAUTIONS** Section in accordance with 21 CFR 201.57 (f)(9)(v) and 201.57(f)(10) respectively.

We have completed the review of these supplemental applications, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling text. Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Provide Regulatory Submissions in Electronic Format – NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submission should be designated "FPL for approved supplements:

NDA 16-921/S021/022/025
NDA 17-340/S032/033/036
NDA 17-522/S022/023/026
NDA 17-579/S018/020/023
NDA 17-955/S019/020/023
NDA 19-049/S007/008/011".

Approval of these submissions by the FDA is not required before the labeling is used.
If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Kalyani Bhatt, Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products,
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Markham Luke
6/10/02 11:40:52 AM
Acting for Dr. Jonathan Wilkin, Division Director, DDDDP

EXHIBIT 38

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-777

FINAL PRINTED LABELING

Fujisawa

Issued: December 2000

PROTOPIC®

(tacrolimus)

Ointment 0.03%

Ointment 0.1%

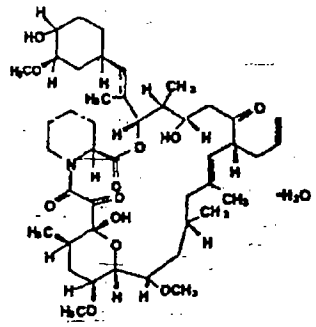
FOR DERMATOLOGIC USE ONLY

APPEARS THIS WAY
ON ORIGINAL

NOT FOR OPHTHALMIC USE

DESCRIPTION:

PROTOPIC (tacrolimus) Ointment contains tacrolimus, a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. It is for topical dermatologic use only. Chemically, tacrolimus is designated as [3*S*-[3*R**[*E*(1*S**,3*S**,4*S**)],4*S**,5*R**,8*S**,9*E*,12*R**,14*R**,15*S**,16*R**,18*S**,19*S**,26a*R**]]-5,6,8,11,12,13,14,15,16,17,18,19,24, 25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate. It has the following structural formula:



APPEARS THIS WAY
ON ORIGINAL

Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12}\bullet H_2O$ and a formula weight of 822.05. Each gram of PROTOPIC Ointment contains (w/w) either 0.03% or 0.1% of tacrolimus in a base of mineral oil, paraffin, propylene carbonate, white petrolatum and white wax.

CLINICAL PHARMACOLOGY:

Mechanism of Action

The mechanism of action of tacrolimus in atopic dermatitis is not known. While the following have been observed, the clinical significance of these observations in atopic dermatitis is not known. It has been demonstrated that tacrolimus inhibits T-lymphocyte activation by first binding to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin is inhibited. This effect has been shown to prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). Tacrolimus also inhibits the transcription for genes which encode IL-3, IL-4, IL-5, GM-CSF, and TNF-α, all of which are involved in the early stages of T-cell activation. Additionally, tacrolimus has been shown to inhibit the release of pre-formed mediators from skin mast cells and

basophils, and to down regulate the expression of FcεRI on Langerhans cells.

Pharmacokinetics

The pooled results from two pharmacokinetic studies in 49 adult atopic dermatitis patients indicate that tacrolimus is absorbed after the topical application of 0.1% PROTOPIC Ointment. Peak tacrolimus blood concentrations ranged from undetectable to 20 ng/mL after single or multiple doses of 0.1% PROTOPIC Ointment, with 45 of the 49 patients having peak blood concentrations less than 5 ng/mL. The results from a pharmacokinetic study of 0.1% PROTOPIC Ointment in 20 pediatric atopic dermatitis patients (ages 6-13 years), show peak tacrolimus blood concentrations below 1.6 ng/mL in all patients.

There was no evidence based on blood concentrations that tacrolimus accumulates systemically upon intermittent topical application for periods of up to 1 year. The absolute bioavailability of topical tacrolimus is unknown. Using IV historical data for comparison, the bioavailability of tacrolimus from PROTOPIC in atopic dermatitis patients is less than 0.5%. In adults with an average of 53% BSA treated, exposure (i.e., AUC) of tacrolimus from PROTOPIC is approximately 30-fold less than that seen with oral immunosuppressive doses in kidney and liver transplant patients. The lowest tacrolimus blood level at which systemic effects can be observed is not known.

CLINICAL STUDIES:

Three randomized, double-blind, vehicle-controlled, multi-center, phase 3 studies were conducted to evaluate PROTOPIC Ointment for the treatment of patients with moderate to severe atopic dermatitis. One (Pediatric) study included 351 patients 2-15 years of age, and the other two (Adult) studies included a total of 632 patients 15-79 years of age. Fifty-five percent (55%) of the patients were women and 27% were black. At baseline, 58% of the patients had severe disease and the mean body surface area (BSA) affected was 46%. Over 80% of patients had atopic dermatitis affecting the face and/or neck region. In these studies, patients applied either PROTOPIC Ointment 0.03%, PROTOPIC Ointment 0.1%, or vehicle ointment twice daily to 10% - 100% of their BSA for up to 12 weeks.

In the pediatric study, a significantly greater ($p < 0.001$) percentage of patients achieved at least 90% improvement based on the physician's global evaluation of clinical response (the pre-defined primary efficacy end point) in the PROTOPIC Ointment 0.03% treatment group compared to the vehicle treatment group, but there was insufficient evidence that PROTOPIC Ointment 0.1% provided more efficacy than PROTOPIC Ointment 0.03%.

In both adult studies, a significantly greater ($p < 0.001$) percentage of patients achieved at least 90% improvement based on the physician's global evaluation of clinical response in the PROTOPIC Ointment 0.03% and PROTOPIC Ointment 0.1% treatment groups compared to the vehicle treatment group. There was evidence that PROTOPIC Ointment 0.1% may provide more efficacy than PROTOPIC Ointment 0.03%. The difference in efficacy between PROTOPIC Ointment 0.1% and 0.03% was particularly evident in adult patients with severe disease at baseline, adults with extensive BSA involvement, and black adults. Response rates for each treatment group are shown below by age groups. Because the two adult studies were identically designed, the results from these studies were pooled in this table.

Global improvement over baseline at the end-of-treatment in three phase 3 studies

Physician's Global Evaluation of Clinical Response (% Improvement)	Pediatric Study (2-15 Years of Age)		Adult Studies		
	Vehicle Ointment N = 116	PROTOPIC Ointment 0.03% N = 117	Vehicle Ointment N = 212	PROTOPIC Ointment 0.03% N = 211	PROTOPIC Ointment 0.1% N = 209
100%	4 (3%)	14 (12%)	2 (1%)	21 (10%)	20 (10%)
≥ 90%	8 (7%)	42 (36%)	14 (7%)	58 (28%)	77 (37%)
≥ 75%	18 (16%)	65 (56%)	30 (14%)	97 (46%)	117 (56%)
≥ 50%	31 (27%)	85 (73%)	42 (20%)	130 (62%)	152 (73%)

A statistically significant difference in the percentage of adult patients with ≥ 90% improvement was achieved by week 1 for those treated with PROTOPIC Ointment 0.1%, and by week 3 for those treated with PROTOPIC Ointment 0.03%. A statistically significant difference in the percentage of pediatric patients with ≥ 90% improvement was achieved by week 2 for those treated with PROTOPIC Ointment 0.03%.

In adult patients who had achieved ≥ 90% improvement at the end of treatment, 35% of those treated with PROTOPIC Ointment 0.03% and 41% of those treated with PROTOPIC Ointment 0.1%, regressed from this state of improvement at 2 weeks after end-of-treatment. In pediatric patients who had achieved ≥ 90% improvement, 54% of those treated with PROTOPIC Ointment 0.03% regressed from this state of improvement at 2 weeks after end-of-treatment. Because patients were not followed for longer than 2 weeks after end-of-treatment, it is not known how many additional patients regressed at periods longer than 2 weeks after cessation of therapy.

In both PROTOPIC Ointment treatment groups in adults and in the PROTOPIC Ointment 0.03% treatment group in pediatric patients, a significantly greater improvement compared to vehicle ($p < 0.001$) was observed in the secondary efficacy endpoints of percent body surface area involved, patient evaluation of pruritus, erythema, edema, excoriation, oozing, scaling, and lichenification. The following two graphs depict the time course of improvement in the percent body surface area affected in adult and in pediatric patients as a result of treatment.

Figure 1 - Adult Patients Body Surface Area Over Time

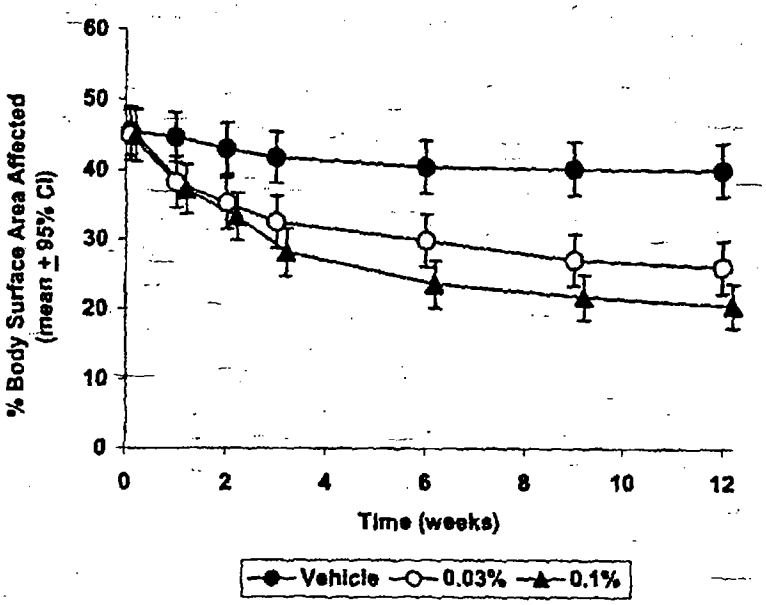
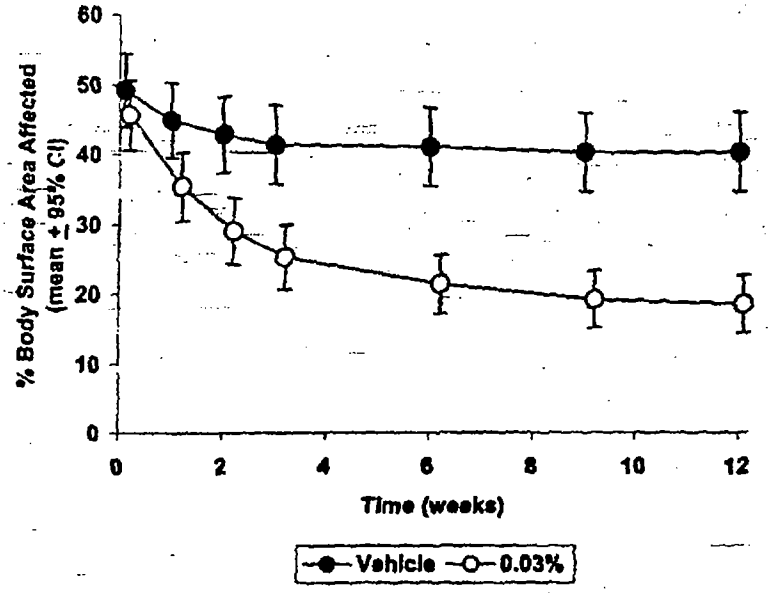
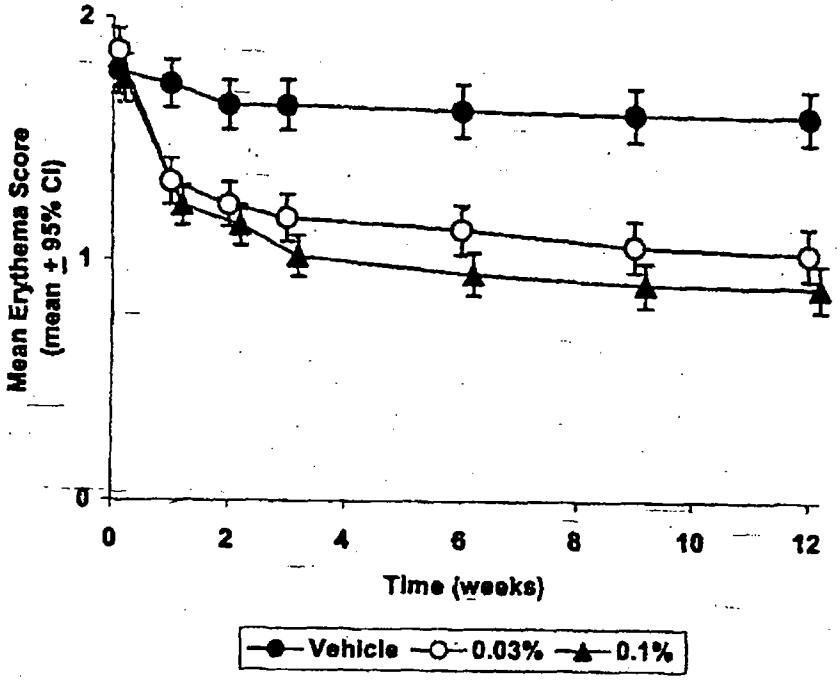


Figure 2 – Pediatric Patients Body Surface Area Over Time



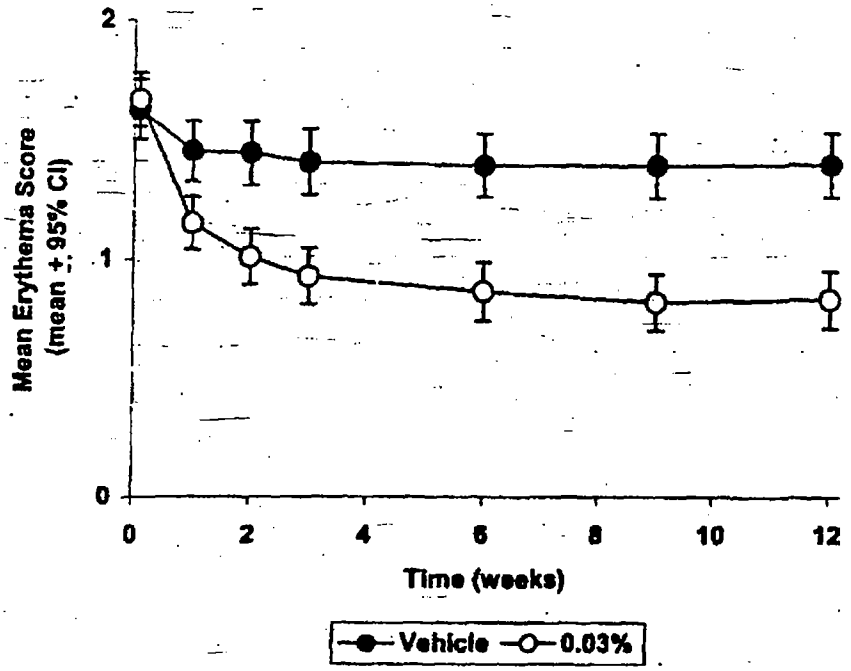
The following two graphs depict the time-course of improvement in erythema in adult and in pediatric patients as a result of treatment.

Figure 3 - Adult Patients Mean Erythema Over Time



APPEARS THIS WAY
ON ORIGINAL

Figure 4 - Pediatric Patients Mean Erythema Over Time



The time course of improvement in the remaining secondary efficacy variables was similar to that of

erythema, with improvement in lichenification slightly slower.

A total of 571 patients applied PROTOPIC Ointment 0.1% in long-term adult and pediatric safety studies for up to one year. In the adult study, 246 patients were evaluated for at least 6 months and 68 patients for 12 months. In the pediatric study, 219 patients were evaluated for at least 6 months and 180 patients for 12 months. On average, patients received treatment for 87% of study days.

INDICATIONS AND USAGE:
PROTOPIC Ointment, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, is indicated for short term and intermittent long term therapy in the treatment of patients with moderate to severe atopic dermatitis in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or are intolerant of alternative, conventional therapies.

CONTRAINDICATIONS:
PROTOPIC Ointment is contraindicated in patients with a history of hypersensitivity to tacrolimus or any other component of the preparation.

PRECAUTIONS:
General

Studies have not evaluated the safety and efficacy of PROTOPIC Ointment in the treatment of clinically infected atopic dermatitis. Before commencing treatment with PROTOPIC Ointment, clinical infections at treatment sites should be cleared.

While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption), treatment with PROTOPIC Ointment may be associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum. In the presence of these infections, the balance of risks and benefits associated with PROTOPIC Ointment use should be evaluated.

In clinical studies, 33 cases of lymphadenopathy (0.8%) were reported and were usually related to infections (particularly of the skin) and noted to resolve upon appropriate antibiotic therapy. Of these 33 cases, the majority had either a clear etiology or were known to resolve. Transplant patients receiving immunosuppressive regimens (e.g., systemic tacrolimus) are at increased risk for developing lymphoma; therefore, patients who receive PROTOPIC Ointment and who develop lymphadenopathy should have the etiology of their lymphadenopathy investigated. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, discontinuation of PROTOPIC Ointment should be considered. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.

The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans (see **ADVERSE REACTIONS**), PROTOPIC Ointment shortened the time to skin tumor formation in an animal photocarcinogenicity study (see **Carcinogenesis, Mutagenesis, Impairment of Fertility**). Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure.

The use of PROTOPIC Ointment may cause local symptoms such as skin burning (burning sensation, stinging, soreness) or pruritus. Localized symptoms are most common during the first few days of PROTOPIC Ointment application and typically improve as the lesions of atopic dermatitis heal. With PROTOPIC Ointment 0.1%, 90% of the skin burning events had a duration between 2 minutes and 3 hours (median 15 minutes). Ninety percent of the pruritus events had a duration between 3 minutes and 10 hours (median 20 minutes).

The use of PROTOPIC Ointment in patients with Netherton's Syndrome is not recommended due to the potential for increased systemic absorption of tacrolimus. The safety of PROTOPIC Ointment has not been established in patients with generalized erythroderma.

Information for Patients

(See patient package insert)

Patients using PROTOPIC Ointment should receive the following information and instructions:

1. Patients should use PROTOPIC Ointment as directed by the physician. PROTOPIC Ointment is for external use only. As with any topical medication, patients or caregivers should wash hands after application if hands are not an area for treatment.
2. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using PROTOPIC Ointment.
3. Patients should not use this medication for any disorder other than that for which it was prescribed.
4. Patients should report any signs of adverse reactions to their physician.
5. Before applying PROTOPIC Ointment after a bath or shower, be sure your skin is completely dry.

Drug Interactions

Formal topical drug interaction studies with PROTOPIC Ointment have not been conducted. Based on its minimal extent of absorption, interactions of PROTOPIC Ointment with systemically administered drugs are unlikely to occur but cannot be ruled out. The concomitant administration of known CYP3A4 inhibitors in patients with widespread and/or erythrodermic disease should be done with caution. Some examples of such drugs are erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers and cimetidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) *in vitro* assays of mutagenicity, the *in vitro* CHO/HGPRT assay of mutagenicity, or *in vivo* clastogenicity assays performed in mice. Tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes.

Oral (feed) carcinogenicity studies have been carried out with systemically administered tacrolimus in male and female rats and mice. In the 80-week mouse study and in the 104-week rat study no relationship of tumor incidence to tacrolimus dosage was found at daily doses up to 3 mg/kg [9X the Maximum Recommended Human Dose (MRHD) based on AUC comparisons] and 5 mg/kg (3X the MRHD based on AUC comparisons), respectively.

A 104 week dermal carcinogenicity study was performed in mice with tacrolimus ointment (0.03% - 3%), equivalent to tacrolimus doses of 1.1-118 mg/kg/day or 3.3-354 mg/m^2/day. In the study, the incidence of skin tumors was minimal and the topical application of tacrolimus was not associated with skin tumor formation under ambient room lighting. However, a statistically significant elevation in the incidence of pleomorphic lymphoma in high dose male (25/50) and female animals (27/50) and in the incidence of undifferentiated lymphoma in high dose female animals (13/50) was noted in the mouse

dermal carcinogenicity study. Lymphomas were noted in the mouse dermal carcinogenicity study at a daily dose of 3.5 mg/kg (0.1% tacrolimus ointment) (26X MRHD based on AUC comparisons). No drug-related tumors were noted in the mouse dermal carcinogenicity study at a daily dose of 1.1 mg/kg (0.03% tacrolimus ointment) (10X MRHD based on AUC comparisons).

In a 52-week photocarcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing with concurrent exposure to UV radiation (40 weeks of treatment followed by 12 weeks of observation) with tacrolimus ointment at ≥0.1% tacrolimus.

Reproductive toxicology studies were not performed with topical tacrolimus. In studies of oral tacrolimus no impairment of fertility was seen in male and female rats. Tacrolimus, given orally at 1.0 mg/kg [0.12X MRHD based on body surface area (BSA)] to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and with adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryolethal effects were indicated by a higher rate of pre-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (0.43X MRHD based on BSA), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.

Pregnancy:

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies of topically administered tacrolimus in pregnant women. The experience with PROTOPIC Ointment when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

Reproduction studies were carried out with systemically administered tacrolimus in rats and rabbits. Adverse effects on the fetus were observed mainly at oral dose levels that were toxic to dams. Tacrolimus at oral doses of 0.32 and 1.0 mg/kg (0.04X - 0.12X MRHD based on BSA) during organogenesis in rabbits was associated with maternal toxicity as well as an increase in incidence of abortions. At the higher dose only, an increased incidence of malformations and developmental variations was also seen. Tacrolimus, at oral doses of 3.2 mg/kg during organogenesis in rats, was associated with maternal toxicity and caused an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tacrolimus, given orally at 1.0 and 3.2 mg/kg (0.04X – 0.12X MRHD based on BSA) to pregnant rats after organogenesis and during lactation, was associated with reduced pup weights.

No reduction in male or female fertility was evident.

There are no adequate and well-controlled studies of systemically administered tacrolimus in pregnant women. Tacrolimus is transferred across the placenta. The use of systemically administered tacrolimus during pregnancy has been associated with neonatal hyperkalemia and renal dysfunction. PROTOPIC Ointment should be used during pregnancy only if the potential benefit to the mother justifies a potential risk to the fetus.

Nursing Mothers

Although systemic absorption of tacrolimus following topical applications of PROTOPIC Ointment is minimal relative to systemic administration, it is known that tacrolimus is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from tacrolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

PROTOPIC Ointment 0.03% may be used in pediatric patients 2 years of age and older. Two phase 3 pediatric studies were conducted involving 606 patients 2-15 years of age: one 12-week randomized vehicle-controlled study and one open-label, 1 year, long-term safety study. Three hundred and thirty (330) of these patients were 2 to 6 years of age.

The most common adverse events associated with PROTOPIC Ointment application in pediatric patients were skin burning and pruritus (see **ADVERSE REACTIONS**). In addition to skin burning and pruritus, the less common events (< 5%) of varicella zoster (mostly chicken pox), and vesiculobullous rash were more frequent in patients treated with PROTOPIC Ointment 0.03% compared to vehicle. In the long-term 1 year safety study involving 255 pediatric patients using PROTOPIC Ointment, the incidence of adverse events, including infections, did not increase with increased duration of study drug exposure or amount of ointment used. In 491 pediatric patients treated with PROTOPIC Ointment, 3(0.6%) developed eczema herpeticum. Since the safety and efficacy of PROTOPIC Ointment have not been established in pediatric patients below 2 years of age, its use in this age group is not recommended.

Geriatric Use

Twenty-five (25) patients ≥ 65 years old received PROTOPIC Ointment in phase 3 studies. The adverse event profile for these patients was consistent with that for other adult patients.

ADVERSE REACTIONS:

No phototoxicity and no photoallergenicity was detected in clinical studies of 12 and 216 normal volunteers, respectively. One out of 198 normal volunteers showed evidence of sensitization in a contact sensitization study.

In three randomized vehicle-controlled studies and two long-term safety studies, 655 and 571 patients respectively, were treated with PROTOPIC Ointment.

The following table depicts the adjusted incidence of adverse events pooled across the 3 identically designed 12 week studies for patients in vehicle, PROTOPIC Ointment 0.03%, and PROTOPIC Ointment 0.1% treatment groups, and the unadjusted incidence of adverse events in two one year long-term safety studies, regardless of relationship to study drug.

Incidence Of Treatment Emergent Adverse Events

	12-Week, Randomized, Double-Blind, Phase 3 Studies 12-Week Adjusted Incidence Rate (%)					Open-Label Studies (up to 1 year) 0.1% Tacrolimus Ointment Incidence(%)	
	Adult			Pediatric		Adult	Pediatric
	Vehicle n=212	0.03% Tacrolimus Ointment n=210	0.1% Tacrolimus Ointment n=209	Vehicle n=116	0.03% Tacrolimus Ointment n=118	n=316	n=255
Skin Burning†	26	46	58	29	43	47	26
Pruritus†	37	46	46	27	41	25	25
Flu-like symptoms†	19	23	31	25	28	22	35
Allergic Reaction	8	12	6	8	4	22	15
Skin Erythema	20	25	28	13	12	12	9
Headache†	11	20	19	8	5	10	18
Skin Infection	11	12	5	14	10	11	11
Fever	4	4	1	13	21	2	18
Infection	1	1	2	9	7	14	8
Cough Increased	2	1	1	14	18	3	15
Asthma	4	6	4	6	6	5	16
Herpes Simplex	4	4	4	2	0	12	5
Eczema Herpeticum	0	1	1	0	2	2	0
Pharyngitis	3	3	4	11	6	5	10
Accidental Injury	4	3	6	3	6	4	12
Pustular Rash	2	3	4	3	2	6	8
Folliculitis†	1	6	4	0	2	11	2
Rhinitis	4	3	2	2	6	5	5
Otitis Medi.	4	0	1	6	12	1	7
Sinusitis†	1	4	2	8	3	3	7
Diarrhea	3	3	4	2	5	4	6
Urticaria	3	3	6	1	1	5	5
Lack of Drug Effect	1	1	0	1	1	10	2
Bronchitis	0	2	2	3	3	3	6
Vomiting	0	1	1	7	6	1	5
Maculopapular Rash	2	2	2	3	0	4	3
Rash†	1	5	2	4	2	2	5
Abdominal Pain	3	1	1	2	3	1	5
Fungal Dermatitis	0	2	1	3	0	2	6
Gastroenteritis	1	2	2	3	0	4	2
Alcohol Intolerance†	0	3	7	0	0	6	0
Acne†	2	4	7	1	0	2	4
Sunburn	1	2	1	0	0	4	4
Skin Disorder	2	2	1	1	4	1	4
Conjunctivitis	0	2	2	2	1	4	2
Pain	1	2	1	0	1	4	3
Vesiculobullous Rash†	3	3	2	0	4	2	2
Lymphadenopathy	2	2	1	0	3	2	3
Nausea	4	3	2	0	1	1	2
Skin Tingling†	2	3	8	1	2	2	1
Face Edema	2	2	1	2	1	3	1
Dyspepsia†	1	1	4	0	0	1	4
Dry Skin	7	3	3	0	1	0	1
Hyperesthesia†	1	3	7	0	0	3	0
Skin Neoplasm Benign‡‡	1	1	1	0	0	2	3
Back Pain†	0	2	2	1	1	3	1
Peripheral Edema	2	4	3	0	0	2	1

Varicella Zoster/Herpes Zoster† ‡	0	1	0	0	5	1	3
Contact Dermatitis	1	3	3	3	4	1	1
Asthenia	1	2	3	0	0	2	1
Pneumonia	0	1	1	2	0	1	2
Eczema	2	2	2	0	0	3	0
Insomnia	3	4	3	1	1	1	0
Exfoliative Dermatitis	3	3	1	0	0	0	2
Dysmenorrhea	2	4	4	0	0	0	2
Periodontal Abscess	1	0	1	0	0	3	0
Myalgia†	0	3	2	0	0	1	0
Cyst†	0	1	3	0	0	0	0

† May be reasonably associated with the use of this drug product

‡ Four cases of chicken pox in the pediatric 12-week study; 1 case of "zoster of the lip" in the adult 12-week study; 7 cases of chicken pox and 1 case of shingles in the open-label pediatric study; 2 cases of herpes zoster in the open-label adult study.

‡‡ Generally "warts".

Other adverse events which occurred at an incidence greater than or equal to 1% in any clinical study include: alopecia, ALT or AST increased, anaphylactoid reaction, angina pectoris, angioedema, anorexia, anxiety, arrhythmia, arthralgia, arthritis, bilirubinemia, breast pain, cellulitis, cerebrovascular accident, cheilitis, chills, constipation, creatinine increased, dehydration, depression, dizziness, dyspnea, ear pain, ecchymosis, edema, epistaxis, exacerbation of untreated area, eye disorder, eye pain, furunculosis, gastritis, hernia, hyperglycemia, hypertension, hypoglycemia, hypoxia, laryngitis, leukocytosis, leukopenia, liver function tests abnormal, lung disorder, malaise, migraine, neck pain, neuritis, palpitations, paresthesia, peripheral vascular disorder, photosensitivity reaction, procedural complication, routine procedure, skin discoloration, sweating, taste perversion, tooth disorder, unintended pregnancy, vaginal moniliasis, vasodilatation, and vertigo.

OVERDOSAGE:

PROTOPIC Ointment is not for oral use. Oral ingestion of PROTOPIC Ointment may lead to adverse effects associated with systemic administration of tacrolimus. If oral ingestion occurs, medical advice should be sought.

DOSAGE AND ADMINISTRATION:

ADULT

PROTOPIC Ointment 0.03% and 0.1%

Apply a thin layer of PROTOPIC Ointment 0.03% or 0.1% to the affected skin areas twice daily and rub in gently and completely. Treatment should be continued for one week after clearing of signs and symptoms of atopic dermatitis.

The safety of PROTOPIC Ointment under occlusion which may promote systemic exposure, has not been evaluated. **PROTOPIC Ointment 0.03% and 0.1% should not be used with occlusive dressings.**

PEDIATRIC

PROTOPIC Ointment 0.03%

Apply a thin layer of PROTOPIC Ointment 0.03% to the affected skin areas twice daily and rub in gently and completely. Treatment should be continued for one week after clearing of signs and symptoms of atopic dermatitis. The safety of PROTOPIC Ointment under occlusion, which may

promote systemic exposure, has not been evaluated. **PROTOPIC Ointment 0.03% should not be used with occlusive dressings.**

HOW SUPPLIED:

PROTOPIC® (tacrolimus) Ointment 0.03%

NDC 0469-5201-30 Product Code 520130
30 gram laminate tube
NDC 0469-5201-60 Product Code 520160
60 gram laminate tube

PROTOPIC® (tacrolimus) Ointment 0.1%

NDC 0469-5202-30 Product Code 520230
30 gram laminate tube
NDC 0469-5202-60 Product Code 520260
60 gram laminate tube

Store at room temperature 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

Rx only

Fujisawa Healthcare, Inc.
Deerfield, IL 60015-2548

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Patient Information
About
PROTOPIC
(tacrolimus)
Ointment

Read this important information before you start using PROTOPIC [pro-TOP-ik] Ointment and each time you refill your prescription. There may be new information. This summary is not meant to take the place of your doctor's advice.

What Is PROTOPIC?
PROTOPIC Ointment is a prescription medicine that is used to treat eczema (atopic dermatitis). It is for adults and children age 2 years and older. You can use PROTOPIC for short or intermittent long periods of treatment. Intermittent means starting and stopping repeatedly, as directed by your doctor. You can use it on all affected areas of your skin, including your face and neck.

Who should not use PROTOPIC?
Do not use PROTOPIC if you are
- breastfeeding
- allergic to PROTOPIC Ointment or any of its ingredients. The active ingredient is tacrolimus. Ask your doctor or pharmacist about the inactive ingredients.

Before you start using PROTOPIC, tell your doctor if you are:
- using any other prescription medicines, non-prescription (over-the-counter) medicines, or supplements
- receiving any form of light therapy (phototherapy, UVA or UVB) on your skin
- using any other type of skin product
- pregnant or planning to become pregnant

How Do I Use PROTOPIC?
Use PROTOPIC only to treat eczema that has been diagnosed by a doctor.
- Wash your hands before using PROTOPIC.
- Apply a thin layer of PROTOPIC to all skin areas that your doctor has diagnosed as eczema. Try to cover the affected areas completely. Most people find that a pea-sized amount squeezed from the tube covers an area about the size of a two-inch circle (approximately the size of a silver dollar).
- Apply the ointment twice a day, about 12 hours apart.
- Before applying PROTOPIC Ointment after a bath or shower, be sure your skin is completely dry.
- Do not cover the skin being treated with bandages, dressings or wraps. Unless otherwise instructed by your doctor, do not apply another type of skin product on top of PROTOPIC Ointment. However, you can wear normal clothing.
- *Do not bathe, shower or swim right after applying PROTOPIC. This could wash off the ointment.*
- If you are a caregiver applying PROTOPIC Ointment to a patient, or if you are a patient who is not treating your hands, wash your hands with soap and water after applying PROTOPIC. This should remove any ointment left on the hands.
- Use PROTOPIC only on your skin. Do not swallow PROTOPIC.

Because 2 strengths of PROTOPIC are available for adult patients, your doctor will decide what strength of PROTOPIC Ointment is best for you.

Many people notice that their skin starts to improve after the first few weeks of treatment. Even though your skin looks and feels better, it is important to keep using PROTOPIC as instructed by your doctor. If you do not notice an improvement in your eczema or if your eczema gets worse within the first few weeks of treatment, tell your doctor.

What Should I Avoid While Using PROTOPIC?

- Avoid sunlight and sun lamps, tanning beds, and treatment with UVA or UVB light. If you need to be outdoors after applying PROTOPIC, wear loose fitting clothing that protects the treated area from the sun. In addition, ask your doctor what other type of protection from the sun you should use.
- Check with your doctor or pharmacist before you
  - start taking any new medicines while using PROTOPIC.
  - start using any other ointment, lotions, or creams on your skin.

What Are The Possible Side Effects of PROTOPIC?

The most common side effects of PROTOPIC are stinging, soreness, a burning feeling, or itching of the skin treated with PROTOPIC. These side effects are usually mild to moderate, are most common during the first few days of treatment and typically lessen if your skin heals.

Less common side effects include acne, swollen or infected hair follicles, headache, increased sensitivity of the skin to hot or cold temperatures, or flu-like symptoms (common cold and congestion (stuffy nose)). Some people may get skin tingling, upset stomach, herpes zoster (chicken pox or shingles), or muscle pain. While you are using PROTOPIC, drinking alcohol may cause the skin or face to become flushed or red and feel hot. Call your doctor if side effects continue or become a problem.

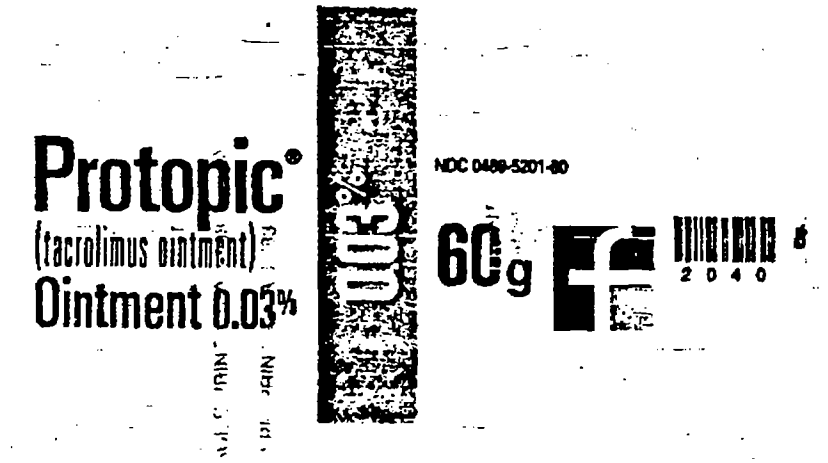
How Should I Store PROTOPIC?

Store PROTOPIC at room temperature (59° to 86°F). For instance, never leave PROTOPIC in your car in cold or hot weather. Make sure the cap on the tube is tightly closed. Keep PROTOPIC out of the reach of children.

General Advice about Prescription Medicines

Do not use PROTOPIC for a condition for which it was not prescribed. If you have any concerns about PROTOPIC, ask your doctor. Your doctor or pharmacist can give you information about PROTOPIC that was written for health care professionals. For more information, you can also visit the Fujisawa Internet site at www.fujisawa.com or call the PROTOPIC Help Line at 1-800-727-7003.

Fujisawa Healthcare, Inc.
Deerfield, IL 60015, www.fujisawa.com



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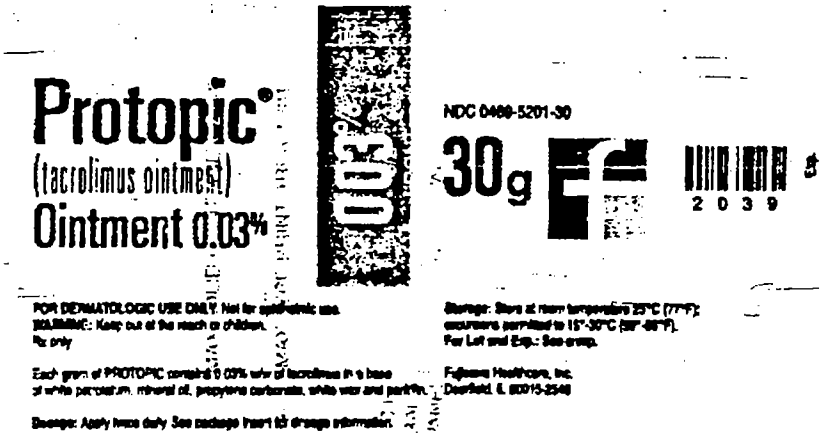

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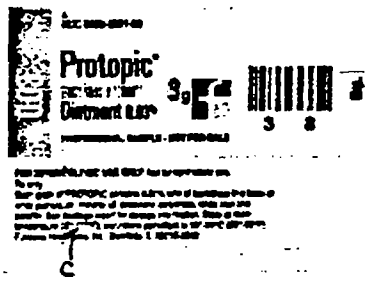

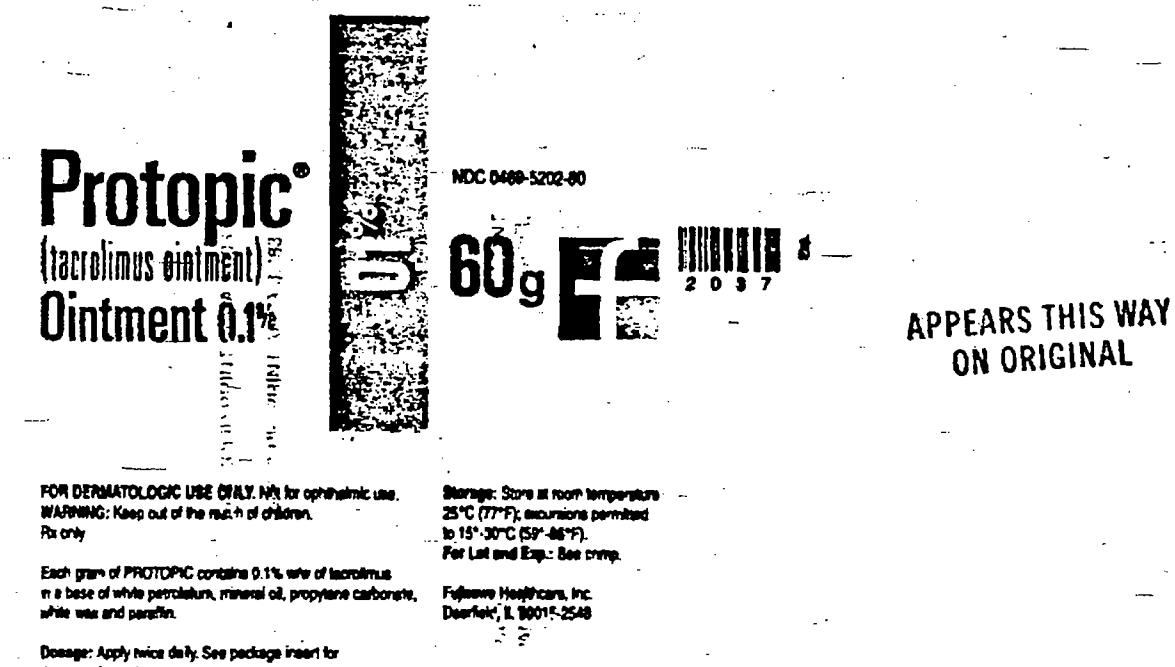

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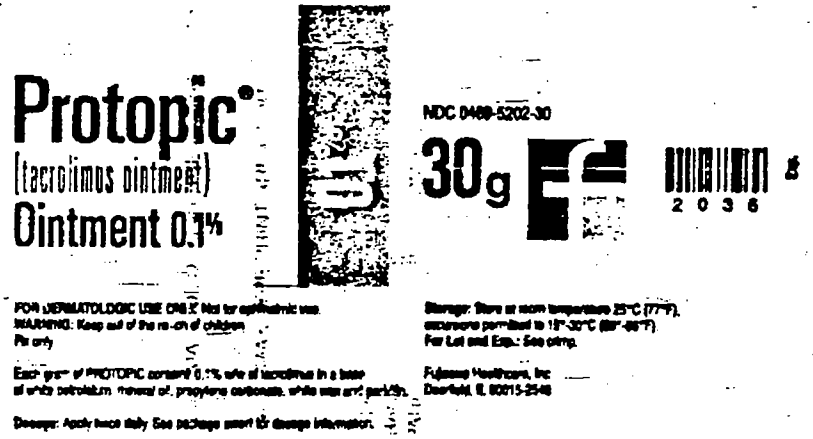

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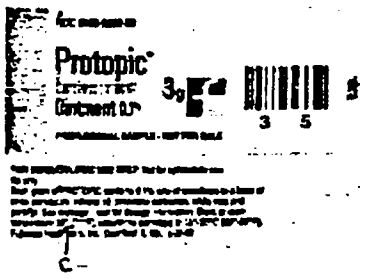


EXHIBIT 39

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 50-777

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

K1.1

K1.1

M Casey 1:15
Rec'd
2-13-00

N50777

N50777

DEC 18 2000

Rec'd
12/13/00
1:15PM

Fujisawa Healthcare, Inc.
Attention: Donald E. Baker, JD
Senior Director, Regulatory Affairs
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548

Dear Mr. Baker:

Please refer to your new drug application (NDA) dated September 8, 1999, received September 9, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Protopic (tacrolimus) Ointment, 0.03 and 0.1%.

We acknowledge receipt of your submissions dated October 21, November 9 and December 9, 1999; January 10 and 31, February 11, March 13, 17 and 29, April 7 and 21, May 18, June 2 and 28, August 21, October 2, November 7, 9, 10 (2), 28 and 30 December 2, 4, 7 (2) and 8, 2000.

This new drug application provides for the use of Protopic (tacrolimus) Ointment, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, for short term and intermittent, long term therapy in the treatment of patients with moderate to severe atopic dermatitis in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or intolerant of alternative, conventional therapies.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 50-777." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your post marketing commitments specified in your facsimile dated December 7, 2000. These commitments, along with any completion dates agreed upon, are listed below:

1. A commitment to submit a retrospective analysis of the three pivotal phase 3 studies and the long-term open label study in adults (Study 97-0-035, Study 97-0-036, Study 97-0-037, and Study FG-06-12, respectively) to explore which possible demographic and disease factor(s) might be associated with a patient having persistently detectable whole blood levels of tacrolimus. Such factors may include, but not be limited to, baseline covariates (e.g., gender, age, race, disease severity), response to treatment, nature of use (intermittent versus chronic), or intercurrent events during the study. The analysis plan will be provided to the Division for review by February 28, 2001.

2. A commitment to conduct a registry study of pediatric patients with atopic dermatitis to address the risk of developing cutaneous or systemic malignancies in patients who have long term intermittent treatment with Protopic Ointment 0.03% or 0.01%. The proposal for this study will be provided to the Division for review by June 30, 2001.

3. A commitment to characterize the comparative bioavailability of Protopic Ointment 0.03% and 0.1% in the long term intermittent treatment of atopic dermatitis. The comparative bioavailability can be characterized by conducting a randomized study in adult patients with moderate to severe atopic dermatitis to measure the comparative pharmacokinetics of Protopic Ointment 0.03% and 0.1%. Blood samples should be collected when the subjects' degree of disease and extent of treatment is consistent with that expected during intermittent long term use. The protocol for this study will be provided to the Division for review by February 28, 2001.

4. A commitment to conduct a pharmacokinetic study with the 0.03% Protopic Ointment in the pediatric patient population between the ages of 2-5 years with moderate to severe atopic dermatitis. The study design could be similar to that of Study FG-06-23 with a minimum of 2 weeks duration, where pharmacokinetic parameters could be evaluated on Day 1 and Day 14, with at least 4 blood samples per sampling day. The blood samples could be collected and analyzed by any of the following techniques:

   a. Sparse sampling approach could be taken so that the entire range of plasma concentration time profile is covered with at least 3 samples per time point. If the sparse sampling approach is chosen, standardization of BSA involvement and disease severity would need to be adopted.
   b. Using data from the previous pediatric studies, a pharmacokinetic sampling program could be developed that would have the blood samples drawn at those time points that were identified to have the highest likelihood of positive blood levels of tacrolimus following dosing.

No matter which approach of collecting blood samples is selected information on the body surface area involvement, disease severity and the amount of ointment applied should be reported. The protocol for this study will be provided to the Division for review by February 28, 2001.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your post marketing commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report.

For administrative purposes, all submissions, including labeling supplements, relating to these post marketing commitments must be clearly designated "Post Marketing Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). Your application contained pediatric studies supporting the safety and efficacy of Protopic Ointment, 0.03% for ages 2 to 15 years. However, you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27) in ages 3 to 23 months. You have agreed as a Phase 4 commitment to submit a protocol by February 28, 2001 for a pharmacokinetic study with the 0.03% Protopic Ointment in the pediatric patient population between the ages of 2-5 years with moderate to severe atopic dermatitis. We are deferring submission of additional study(ies) in pediatric patients aged 3 to 23 months until submission of this pharmacokinetic study report by June 1, 2002. However, in the interim, please submit your pediatric drug development plans within 120 days of the date of this letter. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Millie Wright, Project Manager, at (301) 827-2020.

Sincerely,

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosures

APPEARS THIS WAY
ON ORIGINAL

EXHIBIT 40

ALDARA™

[al dar' a]

(imiquimod)

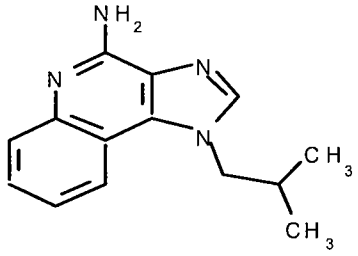
Cream, 5%

For Dermatologic Use Only

Not for Ophthalmic Use

DESCRIPTION

Aldara™ is the brand name for imiquimod which is an immune response modifier. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base consisting of isostearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben.
Chemically, imiquimod is 1-(2-methylpropyl)-1*H*-imidazo[4,5-c]quinolin-4-amine. Imiquimod has a molecular formula of $C_{14}H_{16}N_4$ and a molecular weight of 240.3. Its structural formula is:



CLINICAL PHARMACOLOGY

Pharmacodynamics

Actinic Keratosis

The mechanism of action of Aldara Cream in treating actinic keratosis (AK) lesions is unknown. In a study of 18 patients with AK comparing Aldara Cream to vehicle, increases from baseline in week 2 biomarker levels were reported for CD3, CD4, CD8, CD11c, and CD68 for Aldara Cream treated patients; however, the clinical relevance of these findings is unknown.

Superficial Basal Cell Carcinoma

The mechanism of action of Aldara Cream in treating superficial basal cell carcinoma (sBCC) lesions is unknown. An open label study in six subjects with sBCC suggests that treatment with Aldara Cream may increase the infiltration of lymphocytes, dendritic cells, and macrophages into the tumor lesion; however, the clinical significance of these findings is unknown.

External Genital Warts

Imiquimod has no direct antiviral activity in cell culture. A study in 22 patients with genital/perianal warts comparing Aldara Cream and vehicle shows that Aldara Cream induces mRNA encoding cytokines including interferon-α at the treatment site. In addition HPVL1 mRNA and HPV DNA are significantly decreased following treatment. However, the clinical relevance of these findings is unknown.

Pharmacokinetics

Systemic absorption of imiquimod was observed across the affected skin of 12 patients with genital/perianal warts, with an average dose of 4.6 mg. Mean peak drug concentration of approximately 0.4 ng/mL was seen during the study. Mean urinary recoveries of imiquimod and metabolites combined over the whole course of treatment, expressed as percent of the estimated applied dose, were 0.11 and 2.41% in the males and females, respectively.

Systemic absorption of imiquimod across the affected skin of 58 patients with AK was observed with a dosing frequency of 3 applications per week for 16 weeks. Mean peak serum drug concentrations at the end of week 16 were approximately 0.1, 0.2, and 3.5 ng/mL for the applications to face (12.5 mg imiquimod, 1 single-use packet), scalp (25 mg, 2 packets) and hands/arms (75 mg, 6 packets), respectively.

Mean Serum Imiquimod Concentration Following Administration of the Last Topical Dose During Week 16	
Amount of Aldara Cream applied	**Mean peak serum imiquimod concentration [Cmax]**
12.5 mg (1 packet)	0.1 ng/mL
25 mg (2 packets)	0.2 ng/mL
75 mg (6 packets)	3.5 ng/mL

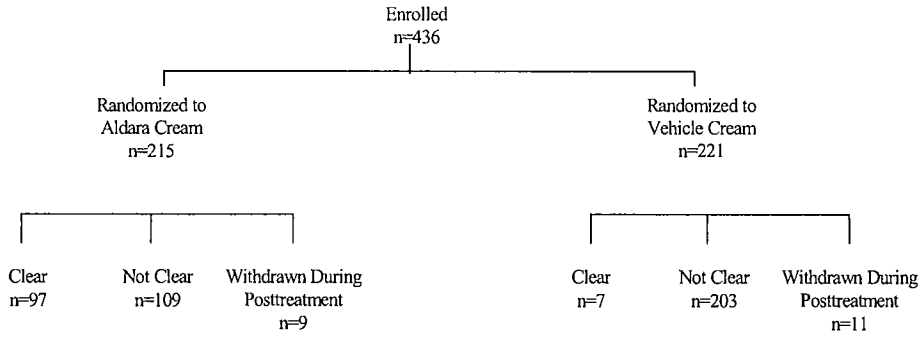
The application surface area was not controlled when more than one packet was used. Dose proportionality was not observed. However it appears that systemic exposure may be more dependent on surface area of application than amount of applied dose. The apparent half-life was approximately 10 times greater with topical dosing than the 2 hour apparent half-life seen following subcutaneous dosing, suggesting prolonged retention of drug in the skin. Mean urinary recoveries of imiquimod and metabolites combined were 0.08 and 0.15% of the applied dose in the group using 75 mg (6 packets) for males and females, respectively following 3 applications per week for 16 weeks.

CLINICAL STUDIES

Actinic Keratosis

In two double-blind, vehicle-controlled clinical studies, 436 patients with actinic keratosis (AK) were treated with Aldara Cream or vehicle cream 2 times per week for 16 weeks. Patients with 4 to 8 clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AK lesions within a 25 cm^2 contiguous treatment area on either the face or scalp were enrolled and randomized to active or vehicle treatment. The population studied ranged from 37-88 years of age (median 66 years) and 55% had Fitzpatrick skin type I or II. All imiquimod-treated patients were Caucasians. The 25 cm^2 contiguous treatment area could be of any dimensions e.g., 5 cm x 5 cm, 3 cm by 8.3 cm, 2 cm by 12.5 cm, etc. On a scheduled dosing day, the study cream was applied to the entire treatment area prior to normal sleeping hours and left on for approximately 8 hours. Twice weekly dosing was continued for a total of 16 weeks. Eight weeks after the patient's last scheduled application of study cream, the clinical response of each patient was evaluated. The primary efficacy variable was the complete clearance rate. Complete clearance (designated below as "clear") was defined as the proportion of subjects at the 8-week post-treatment visit with no (zero) clinically visible AK lesions in the treatment area. Complete clearance included clearance of all baseline lesions, as well as any new or subclinical AK lesions which appeared during therapy. Patient outcomes are shown in the figure below.

Patient Accountability - Combined Phase III Studies
2X/Week Application



Complete and partial clearance rates are shown in the table below. The partial clearance rate was defined as the percentage of patients in whom 75% or more baseline AK lesions were cleared.

Complete Clearance Rates (100% Lesions Cleared)

Study	Aldara Cream	Vehicle
Study A	46% (49/107)	3% (3/110)
Study B	44% (48/108)	4% (4/111)

Partial Clearance Rates (75% or More Baseline Lesions Cleared)

Study	Aldara Cream	Vehicle
Study A	60% (64/107)	10% (11/110)
Study B	58% (63/108)	14% (15/111)

Sub-clinical AK lesions may become apparent in the treatment area during treatment with Aldara Cream. During the course of treatment, 48% (103/215) of patients experienced an increase in AK lesions relative to the number present at baseline within the treatment area. Patients with an increase in AK lesions had a similar response to those with no increase in AK lesions.

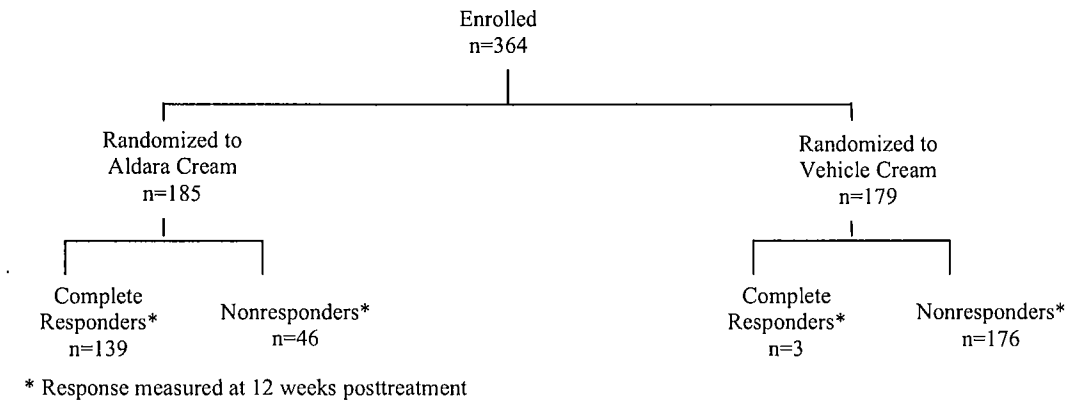
Of the 206 imiquimod subjects with both baseline and 8-week post-treatment scarring assessments, only 6 (2.9%) had a greater degree of scarring scores at 8-weeks post-treatment than at baseline.

SUPERFICIAL BASAL CELL CARCINOMA

In two double-blind, vehicle-controlled clinical studies, 364 patients with primary superficial basal cell carcinoma (sBCC) were treated with Aldara Cream or vehicle cream 5X/week for 6 weeks. Patients with one biopsy-confirmed sBCC tumor were enrolled and randomized in a 1:1 ratio to active or vehicle treatment. Target tumors were to have a minimum area of 0.5 cm^2 and a maximum diameter of 2.0 cm (4.0 cm^2). Target tumors were not to be located within 1.0 cm of the hairline, eyes, nose, mouth, ears, on the anogenital area or on the hands or feet, or have any atypical features. On a scheduled dosing day, the study cream was applied to the target tumor and approximately 1 cm (about 1/3 inch) beyond the target tumor prior to normal sleeping hours; 5X/week dosing was continued for a total of 6 weeks. Twelve weeks after the last scheduled application of study cream, the target tumor area was clinically assessed. The entire target tumor was then excised and examined histologically for the presence of tumor.

The primary efficacy variable was the complete response rate defined as the proportion of patients with clinical (visual) and histological clearance of the sBCC lesion at 12 weeks post-treatment. The population ranged from 31-89 years of age (median 60 years) and 65% had Fitzpatrick skin type I or II. Patient outcomes are shown in the figure below.

Patient Accountability - Combined Phase III Studies



* Response measured at 12 weeks posttreatment

OF ALDARA-TREATED PATIENTS 6% (11/178) WHO HAD BOTH CLINICAL AND HISTOLOGICAL ASSESSMENTS POST-TREATMENT, AND APPEARED TO BE CLINICALLY CLEAR IN STUDIES C AND D HAD EVIDENCE OF TUMOR ON EXCISION OF THE CLINICALLY CLEAR TREATMENT AREA.

DATA ON COMPOSITE CLEARANCE (DEFINED AS BOTH CLINICAL AND HISTOLOGICAL CLEARANCE) ARE SHOWN IN THE TABLE BELOW.

COMPOSITE CLEARANCE RATES AT 12 WEEKS POST-TREATMENT FOR SUPERFICIAL BASAL CELL CARCINOMA 5X/WEEK APPLICATION

STUDY	Aldara CREAM	VEHICLE CREAM
Study C	70% (66/94)	2% (2/89)
Study D	80% (73/91)	1% (1/90)
Total	75% (139/185)	2% (3/179)

An open-label 5-year study (Study E) is ongoing to assess the recurrence of sBCC treated with Aldara Cream applied once daily 5 days per week for 6 weeks. Target tumor inclusion criteria were the same as for Studies C and D as described above. At 12-weeks post-treatment, patients were clinically (no histological assessment) evaluated for evidence of persistent sBCC. Subjects with no clinical evidence of BCC entered the long-term follow-up period. At the 12 week post-treatment assessment 163/182 (90%) of the subjects enrolled had no clinical evidence of sBCC at their target site and 162 subjects entered the long-term follow-up period for up to 5 years. Two year (24 month) follow-up data are available from this study and are presented in the table below:

Estimated Clinical Clearance Rates for Superficial Basal Cell Carcinoma

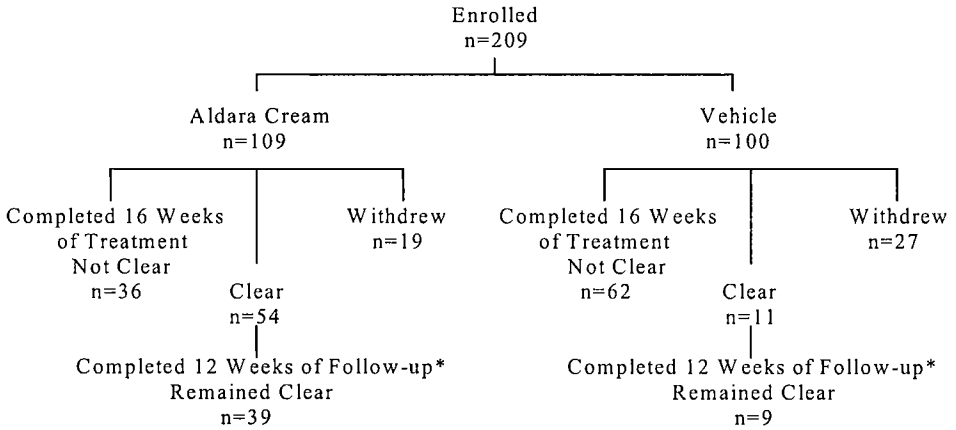
Follow-up Period				
Follow-up visit after 12-week post-treatment assessment	No. of Subjects who remained clinically clear	No. of Subjects with sBCC recurrence	No. of Subjects who discontinued at this visit with no sBCC [a]	Estimated Rate of Patients who Clinically Cleared and remained Clear[b]
Month 3	153	4	5	87%
Month 6	149	4	0	85%
Month 12	143	2	4	84%
Month 24	139	4	0	79%

[a] Reasons for discontinuation included death, non-compliance, entry criteria violations, personal reasons, and treatment of nearby sBCC tumor.
[b] Estimated rate of patients who clinically cleared and remained clear are estimated based on the time to event analysis employing the life table method beginning with the rate of clinical clearance at 12 weeks post-treatment.

External Genital Warts

In a double-blind, placebo-controlled clinical study, 209 otherwise healthy patients 18 years of age and older with genital/perianal warts were treated with Aldara Cream or vehicle control 3X/week for a maximum of 16 weeks. The median baseline wart area was 69 mm^2 (range 8 to 5525 mm^2). Patient accountability is shown in the figure below.

Patient Accountability - Study 1004-IMIQ
3X/Week Application



*The other patients were either lost to follow-up or experienced recurrences.

Data on complete clearance are listed in the table below. The median time to complete wart clearance was 10 weeks.

Complete Clearance Rates - Study 1004-IMIQ

Treatment	Patients with Complete Clearance of Warts	Patients Without Follow-up	Patients with Warts Remaining at Week 16
Overall			
Aldara Cream (n =109)	50%	17%	33%
Vehicle (n =100)	11%	27%	62%
Females			
Aldara Cream (n =46)	72%	11%	17%
Vehicle (n =40)	20%	33%	48%
Males			
Aldara Cream (n =63)	33%	22%	44%
Vehicle (n =60)	5%	23%	72%

INDICATIONS AND USAGE

Aldara Cream is indicated for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults.

Aldara Cream is indicated for the topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured. The histological diagnosis of superficial basal cell carcinoma should be established prior to treatment, since safety and effectiveness of Aldara Cream have not been established for other types of basal cell carcinomas, including nodular, morpheaform (fibrosing or sclerosing) types.

Aldara Cream is indicated for the treatment of external genital and perianal warts/condyloma acuminata in individuals 12 years old and above.

CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted.

WARNINGS

The diagnosis of sBCC should be confirmed prior to treatment, since safety and effectiveness of Aldara Cream have not been established for other types of basal cell carcinomas, including nodular, morpheaform (fibrosing or sclerosing) types and is not recommended for treatment of BCC subtypes other than the superficial variant (i.e., sBCC). Patients with sBCC treated with Aldara Cream are recommended to have regular follow-up of the treatment site. See table of Estimated Clinical Clearance Rates for Superficial Basal Cell Carcinoma in the CLINICAL STUDIES section.

Aldara Cream has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease and is not recommended for these conditions.

PRECAUTIONS

General

The safety and efficacy of Aldara Cream in immunosuppressed patients have not been established.

Aldara Cream administration is not recommended until the skin is completely healed from any previous drug or surgical treatment.

Aldara Cream has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease.

Aldara Cream should be used with caution in patients with pre-existing autoimmune conditions.

Intense local inflammatory reactions including skin weeping or erosion can occur after only a few applications of Aldara Cream. Local inflammatory reactions may be accompanied, or even preceded, by flu-like systemic signs and symptoms including malaise, fever, nausea, myalgias and rigors. An interruption of dosing should be considered.

Exposure to sunlight (including sunlamps) should be avoided or minimized during use of Aldara Cream because of concern for heightened sunburn susceptibility. Patients should be warned to use protective clothing (hat) when using Aldara Cream. Patients with sunburn should be advised not to use Aldara Cream until fully recovered. Patients who may have considerable sun exposure, e.g., due to their occupation, and those patients with inherent sensitivity to sunlight should exercise caution when using Aldara Cream. Phototoxicity has not been adequately assessed for Aldara Cream. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans *(see ADVERSE REACTIONS)*, Aldara Cream shortened the time to skin tumor formation in an animal photoco-carcinogenicity study *(see Carcinogenesis, Mutagenesis, Impairment of Fertility)*. Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure.

Actinic Keratosis

Safety and efficacy have not been established for Aldara Cream in the treatment of actinic keratosis with repeated use, i.e. more than one treatment course, in the same 25 cm^2 area.

The safety of Aldara Cream applied to areas of skin greater than 25 cm^2 (e.g. 5 cm X 5 cm) for the treatment of actinic keratosis has not been established (*see CLINICAL PHARMACOLOGY; Pharmacokinetics section* regarding systemic absorption).

Superficial Basal Cell Carcinoma

The safety and efficacy of treating superficial basal cell carcinoma (sBCC) lesions on the face, head and anogenital area have not been established.

The efficacy and safety of Aldara Cream have not been established for patients with Basal Cell Nevus Syndrome or Xeroderma Pigmentosum.

Information for Patients

General Information

Patients using Aldara Cream should receive the following information and instructions:

1. This medication is to be used as directed by a physician. It is for external use only. Eye contact should be avoided.

2. The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive.

3. Some reports have been received of localized hypopigmentation and hyperpigmentation following Aldara Cream use. Follow-up information suggests that these skin color changes may be permanent in some patients.

Patients Being Treated for Actinic Keratosis (AK)

1. It is recommended that the treatment area be washed with mild soap and water 8 hours following Aldara Cream application.

2. It is common for patients to experience local skin reactions (can range from mild to severe in intensity) during treatment with Aldara Cream, and these reactions may extend beyond the application site onto the surrounding skin. Skin reactions generally decrease in intensity or resolve after cessation of Aldara Cream therapy. Potential local skin reactions include erythema, edema, vesicles, erosion/ulceration, weeping/exudate, flaking/scaling/dryness, and scabbing/crusting. Most patients using Aldara Cream for the treatment of AK experience erythema, flaking/scaling/dryness and scabbing/crusting at the application site with normal dosing. Patients may also experience application site reactions such as itching and/or burning. Local skin reactions may be of such an intensity that patients may require rest periods from treatment. Treatment with Aldara Cream can be resumed after the skin reaction has subsided, as determined by the physician. Patients should contact their physician promptly if they experience any sign or symptom at the

application site that restricts or prohibits their daily activity or makes continued application of the cream difficult.

3. Because of local skin reactions, during treatment and until healed, the treatment area is likely to appear noticeably different from normal skin. The skin surrounding the treatment area may also be affected, but less intensely so.

4. Contact with the eyes, lips and nostrils should be avoided.

5. Use of sunscreen is encouraged, and patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Aldara Cream.

6. During treatment, sub-clinical AK lesions may become apparent in the treatment area and may subsequently resolve.

7. Partially-used packets should be discarded and not reused.

8. Dosing is twice weekly for the full 16 weeks, unless otherwise directed by the physician. However, the treatment period should not be extended beyond 16 weeks due to missed doses or rest periods.

PATIENTS BEING TREATED FOR SUPERFICIAL BASAL CELL CARCINOMA (SBCC)

1. It is recommended that the treatment area be washed with mild soap and water 8 hours following Aldara Cream application.

2. Most patients using Aldara Cream for the treatment of sBCC experience erythema, edema, induration, erosion, scabbing/crusting and flaking/scaling at the application site with normal dosing. These local skin reactions generally decrease in intensity or resolve after cessation of Aldara Cream therapy. Patients may also experience application site reactions such as itching and/or burning. Local skin reactions may be of such an intensity that patients may require rest periods from treatment. Treatment with Aldara Cream can be resumed after the skin reaction has subsided, as determined by the physician.

3. During treatment and until healed, affected skin is likely to appear noticeably different from normal skin.

4. It is prudent for patients to minimize or avoid exposure to natural or artificial sunlight.

5. The clinical outcome of therapy can be determined after regeneration of the treated skin, approximately 12 weeks after the end of treatment.

6. Patients should contact their physician if they experience any sign or symptom at the application site that restricts or prohibits their daily activity or makes continued application of the cream difficult.

7. Patients with sBCC treated with Aldara Cream are recommended to have regular follow-up to re-evaluate the treatment site.

Patients Being Treated for External Genital Warts

1. It is recommended that the treatment area be washed with mild soap and water 6-10 hours following Aldara Cream application.

2. It is common for patients to experience local skin reactions such as erythema, erosion, excoriation/flaking, and edema at the site of application or surrounding areas. Most skin reactions are mild to moderate. Severe skin reactions can occur and should be promptly reported to the prescribing physician. Should severe local skin reaction occur, the cream should be removed by washing the treatment area with mild soap and water. Treatment with Aldara Cream can be resumed after the skin reaction has subsided.

3. Sexual (genital, anal, oral) contact should be avoided while the cream is on the skin.

4. Application of Aldara Cream in the vagina is considered internal and should be avoided. Female patients should take special care if applying the cream at the opening of the vagina because local skin reactions on the delicate moist surfaces can result in pain or swelling, and may cause difficulty in passing urine.

5. Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.

6. Patients should be aware that new warts may develop during therapy, as Aldara Cream is not a cure.

7. The effect of Aldara Cream on the transmission of genital/perianal warts is unknown.

8. Aldara Cream may weaken condoms and vaginal diaphragms, therefore concurrent use is not recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

*Note: The Maximum Recommended Human Dose (MRHD) was set at 2 packets per treatment of Aldara Cream (25 mg imiquimod) for the animal multiple of human exposure ratios presented in this label. If higher doses than 2 packets of Aldara Cream are used clinically, then the animal multiple of human exposure would be reduced for that dose. A non-proportional increase in systemic exposure with increased dose of Aldara Cream was noted in the clinical pharmacokinetic study conducted in actinic keratosis subjects (*see Pharmacokinetics*). The AUC after topical application of 6 packets of Aldara Cream was 8 fold greater than the AUC after topical application of 2 packets of Aldara Cream in actinic keratosis subjects. Therefore, if a dose of 6 packets per treatment of Aldara Cream was topically administered to an individual, then the animal multiple of human exposure would be either 1/3 of the value provided in the label (based on body surface area comparisons) or 1/8 of the value provided in the label (based on AUC comparisons). The animal multiples of human exposure*

calculations were based on weekly dose comparisons for the carcinogenicity studies described in this label. The animal multiples of human exposure calculations were based on daily dose comparisons for the reproductive toxicology studies described in this label.

In an oral (gavage) rat carcinogenicity study, imiquimod was administered to Wistar rats on a 2X/week (up to 6 mg/kg/day) or daily (3 mg/kg/day) dosing schedule for 24 months. No treatment related tumors were noted in the oral rat carcinogenicity study up to the highest doses tested in this study of 6 mg/kg administered 2X/week in female rats (87X MRHD based on weekly AUC comparisons), 4 mg/kg administered 2X/week in male rats (75X MRHD based on weekly AUC comparisons) or 3 mg/kg administered 7X/week to male and female rats (153X MRHD based on weekly AUC comparisons).

In a dermal mouse carcinogenicity study, imiquimod cream (up to 5 mg/kg/application imiquimod or 0.3% imiquimod cream) was applied to the backs of mice 3X/week for 24 months. A statistically significant increase in the incidence of liver adenomas and carcinomas was noted in high dose male mice compared to control male mice (251X MRHD based on weekly AUC comparisons). An increased number of skin papillomas was observed in vehicle cream control group animals at the treated site only. The quantitative composition of the vehicle cream used in the dermal mouse carcinogenicity study is the same as the vehicle cream used for Aldara Cream, minus the active moiety (imiquimod).

In a 52-week dermal photoco-carcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing (3X/week; 40 weeks of treatment followed by 12 weeks of observation) with concurrent exposure to UV radiation (5 days per week) with the Aldara Cream vehicle alone. No additional effect on tumor development beyond the vehicle effect was noted with the addition of the active ingredient, imiquimod, to the vehicle cream.

Imiquimod revealed no evidence of mutagenic or clastogenic potential based on the results of five in vitro genotoxicity tests (Ames assay, mouse lymphoma L5178Y assay, Chinese hamster ovary cell chromosome aberration assay, human lymphocyte chromosome aberration assay and SHE cell transformation assay) and three in vivo genotoxicity tests (rat and hamster bone marrow cytogenetics assay and a mouse dominant lethal test).

Daily oral administration of imiquimod to rats, throughout mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction, at doses up to 87X MRHD based on AUC comparisons.

Pregnancy

Pregnancy Category C:

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 1, 5 and 20 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. In the presence of maternal toxicity, fetal effects noted at 20 mg/kg/day (577X MRHD based on AUC comparisons) included increased resorptions, decreased fetal body weights, delays in skeletal ossification, bent limb bones, and two fetuses in one litter (2 of 1567 fetuses) demonstrated exencephaly, protruding tongues and low-set ears. No treatment related effects

on embryofetal toxicity or teratogenicity were noted at 5 mg/kg/day (98X MRHD based on AUC comparisons).

Intravenous doses of 0.5, 1 and 2 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 18) to pregnant female rabbits. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 2 mg/kg/day (1.5X MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (407X MRHD based on AUC comparisons).

A combined fertility and peri- and post-natal development study was conducted in rats. Oral doses of 1, 1.5, 3 and 6 mg/kg/day imiquimod were administered to male rats from 70 days prior to mating through the mating period and to female rats from 14 days prior to mating through parturition and lactation. No effects on growth, fertility, reproduction or post-natal development were noted at doses up to 6 mg/kg/day (87X MRHD based on AUC comparisons), the highest dose evaluated in this study. In the absence of maternal toxicity, bent limb bones were noted in the F1 fetuses at a dose of 6 mg/kg/day (87X MRHD based on AUC comparisons). This fetal effect was also noted in the oral rat embryofetal development study conducted with imiquimod. No treatment related effects on teratogenicity were noted at 3 mg/kg/day (41X MRHD based on AUC comparisons).

There are no adequate and well-controlled studies in pregnant women. Aldara Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether topically applied imiquimod is excreted in breast milk.

Pediatric Use

Safety and efficacy in patients with external genital/perianal warts below the age of 12 years have not been established.

AK and sBCC are not conditions generally seen within the pediatric population. The safety and efficacy of Aldara Cream for AK or sBCC in patients less than 18 years of age have not been established.

Geriatric Use

Of the 215 patients in the 2X/week clinical studies evaluating the treatment of AK lesions with Aldara Cream, 127 patients (59%) were 65 years and older, while 60 patients (28%) were 75 years and older. Of the 185 patients in the 5X/week treatment groups of clinical studies evaluating the treatment of sBCC with Aldara Cream, 65 patients (35%) were 65 years and older, while 25 patients (14%) were 75 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients. No other clinical experience has identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Healthcare providers and patients may contact 3M or FDA's Medwatch to report adverse reactions by calling 1-800-814-1795 or 1-800-FDA-1088, or on the internet at http://www.fda.gov/medwatch.

Dermal safety studies involving induction and challenge phases produced no evidence that Aldara Cream causes photoallergenicity or contact sensitization in healthy skin; however, cumulative irritancy testing revealed the potential for Aldara Cream to cause irritation, and in the clinical studies application site reactions were reported in a significant percentage of study patients. Phototoxicity testing was incomplete as wavelengths in the UVB range were not included and Aldara Cream has peak absorption in the UVB range (320 nm) of the light spectrum.

Actinic Keratosis

The data described below reflect exposure to Aldara Cream or vehicle in 436 patients enrolled in two double-blind, vehicle-controlled, 2X/week studies. Patients applied Aldara Cream or vehicle to a 25 cm^2 contiguous treatment area on the face or scalp 2X/week for 16 weeks.

Summary of All Adverse Events Reported by > 1% of Patients in the Combined 2X/ Week Studies

Body System Preferred Term	Imiq 2X/Week (n= 215)	Vehicle 2X/Week (n= 221)
APPLICATION SITE DISORDERS		
APPLICATION SITE REACTION	71 (33.0%)	32 (14.5%)
BODY AS A WHOLE - GENERAL DISORDERS		
BACK PAIN	3 (1.4%)	2 (0.9%)
FATIGUE	3 (1.4%)	2 (0.9%)
FEVER	3 (1.4%)	0 (0.0%)
HEADACHE	11 (5.1%)	7 (3.2%)
HERNIA NOS	4 (1.9%)	1 (0.5%)
INFLUENZA- LIKE SYMPTOMS	4 (1.9%)	4 (1.8%)
PAIN	3 (1.4%)	3 (1.4%)
RIGORS	3 (1.4%)	0 (0.0%)
CARDIOVASCULAR DISORDERS, GENERAL		
CHEST PAIN	1 (0.5%)	4 (1.8%)
HYPERTENSION	3 (1.4%)	5 (2.3%)
CENTR & PERIPH NERVOUS SYSTEM DISORDERS		
DIZZINESS	3 (1.4%)	1 (0.5%)
GASTRO- INTESTINAL SYSTEM DISORDERS		
DIARRHOEA	6 (2.8%)	2 (0.9%)
DYSPEPSIA	6 (2.8%)	4 (1.8%)
GASTROESOPHAGEAL REFLUX	3 (1.4%)	3 (1.4%)
NAUSEA	3 (1.4%)	3 (1.4%)
VOMITING	3 (1.4%)	1 (0.5%)
HEART RATE AND RHYTHM DISORDERS		
FIBRILLATION ATRIAL	3 (1.4%)	2 (0.9%)
METABOLIC AND NUTRITIONAL DISORDERS		
HYPERCHOLESTEROLAEMIA	4 (1.9%)	0 (0.0%)
MUSCULO- SKELETAL SYSTEM DISORDERS		
ARTHRALGIA	2 (0.9%)	4 (1.8%)

ARTHRITIS	2 (0.9%)	3 (1.4%)
MYALGIA	3 (1.4%)	3 (1.4%)
SKELETAL PAIN	1 (0.5%)	3 (1.4%)
NEOPLASM		
BASAL CELL CARCINOMA	5 (2.3%)	5 (2.3%)
CARCINOMA SQUAMOUS	8 (3.7%)	5 (2.3%)
RESISTANCE MECHANISM DISORDERS	9 (4.2%)	11 (5.0%)
HERPES SIMPLEX	4 (1.9%)	4 (1.8%)
INFECTION VIRAL	3 (1.4%)	2 (0.9%)
RESPIRATORY SYSTEM DISORDERS		
BRONCHITIS	2 (0.9%)	3 (1.4%)
COUGHING	6 (2.8%)	10 (4.5%)
PHARYNGITIS	4 (1.9%)	4 (1.8%)
PULMONARY CONGESTION	1 (0.5%)	3 (1.4%)
RHINITIS	7 (3.3%)	8 (3.6%)
SINUSITIS	16 (7.4%)	14 (6.3%)
UPPER RESP TRACT INFECTION	33 (15.3%)	27 (12.2%)
SECONDARY TERMS		
ABRASION NOS	7 (3.3%)	5 (2.3%)
CYST NOS	0 (0.0%)	4 (1.8%)
INFLICTED INJURY	19 (8.8%)	21 (9.5%)
POST- OPERATIVE PAIN	3 (1.4%)	4 (1.8%)
SKIN AND APPENDAGES DISORDERS	47 (21.9%)	42 (19.0%)
ALOPECIA	3 (1.4%)	0 (0.0%)
DERMATITIS	3 (1.4%)	7 (3.2%)
ECZEMA	4 (1.9%)	3 (1.4%)
HYPERKERATOSIS	19 (8.8%)	12 (5.4%)
PHOTOSENSITIVITY REACTION	2 (0.9%)	4 (1.8%)
PRURITUS	2 (0.9%)	3 (1.4%)
RASH	5 (2.3%)	5 (2.3%)
SKIN DISORDER	6 (2.8%)	7 (3.2%)
VERRUCA	1 (0.5%)	3 (1.4%)
URINARY SYSTEM DISORDERS	8 (3.7%)	10 (4.5%)
URINARY TRACT INFECTION	3 (1.4%)	1 (0.5%)
VISION DISORDERS		
CONJUNCTIVITIS	1 (0.5%)	3 (1.4%)
EYE ABNORMALITY	4 (1.9%)	1 (0.5%)
EYE INFECTION	0 (0.0%)	3 (1.4%)

Summary of All Application Site Reactions Reported by > 1% of Patients in the Combined 2X/ Week Studies

Included Term	Imiq 2X/Week (n= 215)	Vehicle 2X/Week (n= 221)
BLEEDING AT TARGET SITE	7 (3.3%)	1 (0.5%)
BURNING AT REMOTE SITE	4 (1.9%)	0 (0.0%)
BURNING AT TARGET SITE	12 (5.6%)	4 (1.8%)
INDURATION AT REMOTE SITE	3 (1.4%)	0 (0.0%)
INDURATION AT TARGET SITE	5 (2.3%)	3 (1.4%)
IRRITATION AT REMOTE SITE	3 (1.4%)	0 (0.0%)
ITCHING AT REMOTE SITE	7 (3.3%)	3 (1.4%)
ITCHING AT TARGET SITE	44 (20.5%)	15 (6.8%)
PAIN AT TARGET SITE	5 (2.3%)	2 (0.9%)
STINGING AT TARGET SITE	6 (2.8%)	2 (0.9%)
TENDERNESS AT TARGET SITE	4 (1.9%)	3 (1.4%)

Local skin reactions were collected independently of the adverse event "application site reaction" in an effort to provide a better picture of the specific types of local reactions that might be seen. The most frequently reported local skin reactions were erythema, flaking/scaling/dryness, and scabbing/crusting. The prevalence and severity of local skin reactions that occurred during controlled studies are shown in the following table.

Local Skin Reactions in the Treatment Area as Assessed by the Investigator (Percentage of Patients) 2X/Week Application

	Mild/Moderate/Severe		Severe	
	Aldara Cream n=215	Vehicle n=220	Aldara Cream n=215	Vehicle N=220
Erythema	209 (97%)	206 (93%)	38 (18%)	5 (2%)
Edema	106 (49%)	22 (10%)	0 (0%)	0 (0%)
Weeping/Exudate	45 (22%)	3 (1%)	0 (0%)	0 (0%)
Vesicles	19 (9%)	2 (1%)	0 (0%)	0 (0%)
Erosion/Ulceration	103 (48%)	20 (9%)	5 (2%)	0 (0%)
Flaking/Scaling/Dryness	199 (93%)	199 (91%)	16 (7%)	7 (3%)
Scabbing/Crusting	169 (79%)	92 (42%)	18 (8%)	4 (2%)

The adverse reactions that most frequently resulted in clinical intervention (e.g., rest periods, withdrawal from study) were local skin and application site reactions. Overall, in the clinical studies, 2% (5/215) of patients discontinued for local skin/application site reactions. Of the 215 patients treated, 35 patients (16%) on Aldara Cream and 3 of 220 patients (1%) on vehicle cream had at least one rest period. Of these Aldara Cream patients, 32 (91%) resumed therapy after a rest period.

In the AK studies, 22 of 678 imiquimod treated patients developed treatment site infections that required a rest period off Aldara Cream and were treated with antibiotics (19 with oral and 3 with topical).

Superficial Basal Cell Carcinoma

THE DATA DESCRIBED BELOW REFLECT EXPOSURE TO ALDARA CREAM OR VEHICLE IN 364 PATIENTS ENROLLED IN TWO DOUBLE-BLIND, VEHICLE-CONTROLLED, 5X/WEEK STUDIES. PATIENTS APPLIED ALDARA CREAM OR VEHICLE 5X/WEEK FOR 6 WEEKS. THE INCIDENCE OF ADVERSE EVENTS REPORTED BY > 1% OF SUBJECTS DURING THE
6 WEEK TREATMENT PERIOD IS SUMMARIZED BELOW.

SUMMARY OF ALL ADVERSE EVENTS REPORTED BY > 1% OF PATIENTS IN THE COMBINED 5X/ WEEK STUDIES

Body System Preferred Term	Imiquimod 5x/Week (n= 185) N %	Vehicle 5x/Week (n= 179) N %
APPLICATION SITE DISORDERS		
APPLICATION SITE REACTION	52 (28.1%)	5 (2.8%)
BODY AS A WHOLE - GENERAL DISORDERS		

ALLERGY AGGRAVATED	2 (1.1%)	1 (0.6%)
BACK PAIN	7 (3.8%)	1 (0.6%)
CHEST PAIN	2 (1.1%)	0 (0.0%)
FATIGUE	4 (2.2%)	2 (1.1%)
FEVER	3 (1.6%)	0 (0.0%)
PAIN	3 (1.6%)	2 (1.1%)
CARDIOVASCULAR DISORDERS, GENERAL		
HYPERTENSION	5 (2.7%)	1 (0.6%)
CENTR & PERIPH NERVOUS SYSTEM DISORDERS		
DIZZINESS	2 (1.1%)	1 (0.6%)
HEADACHE	14 (7.6%)	4 (2.2%)
GASTRO- INTESTINAL SYSTEM DISORDERS		
ABDOMINAL PAIN	1 (0.5%)	2 (1.1%)
DIARRHOEA	1 (0.5%)	2 (1.1%)
DYSPEPSIA	3 (1.6%)	2 (1.1%)
GASTRO- INTESTINAL DISORDER NOS	1 (0.5%)	2 (1.1%)
NAUSEA	2 (1.1%)	0 (0.0%)
TOOTH DISORDER	0 (0.0%)	2 (1.1%)
METABOLIC AND NUTRITIONAL DISORDERS		
GOUT	2 (1.1%)	0 (0.0%)
MUSCULO-SKELETAL SYSTEM DISORDERS		
SKELETAL PAIN	3 (1.6%)	2 (1.1%)
PSYCHIATRIC DISORDERS		
ANXIETY	2 (1.1%)	1 (0.6%)
RESISTANCE MECHANISM DISORDERS		
INFECTION	1 (0.5%)	3 (1.7%)
INFECTION FUNGAL	2 (1.1%)	2 (1.1%)
RESPIRATORY SYSTEM DISORDERS		
COUGHING	3 (1.6%)	1 (0.6%)
PHARYNGITIS	2 (1.1%)	1 (0.6%)
RHINITIS	5 (2.7%)	1 (0.6%)
SINUSITIS	4 (2.2%)	1 (0.6%)
UPPER RESP TRACT INFECTION	6 (3.2%)	2 (1.1%)
SECONDARY TERMS		
INFLICTED INJURY	3 (1.6%)	3 (1.7%)
PROCEDURAL SITE REACTION	2 (1.1%)	3 (1.7%)
SKIN AND APPENDAGES DISORDERS		
HYPERKERATOSIS	3 (1.6%)	2 (1.1%)
RASH	3 (1.6%)	1 (0.6%)
SKIN DISORDER	1 (0.5%)	3 (1.7%)
WHITE CELL AND RES DISORDERS		
LYMPHADENOPATHY	5 (2.7%)	1 (0.6%)

IN CONTROLLED CLINICAL STUDIES, THE MOST FREQUENTLY REPORTED ADVERSE REACTIONS WERE LOCAL SKIN AND APPLICATION SITE REACTIONS INCLUDING ERYTHEMA, EDEMA, INDURATION, EROSION, FLAKING/SCALING, SCABBING/CRUSTING, ITCHING AND BURNING AT THE APPLICATION SITE. THE INCIDENCE OF THE APPLICATION SITE REACTIONS REPORTED BY > 1% OF THE SUBJECTS DURING THE 6 WEEK TREATMENT PERIOD IS SUMMARIZED IN THE TABLE BELOW.

Summary of All Application Site Reactions Reported by > 1% of Patients in the Combined 5X/ Week Studies

Included Term	Imiquimod 5x/ Week (n= 185) N %	Vehicle 5x/ Week (n= 179) N %
ITCHING AT TARGET SITE	30 (16.2%)	1 (0.6%)
BURNING AT TARGET SITE	11 (5.9%)	2 (1.1%)

PAIN AT TARGET SITE	6 (3.2%)	0 (0.0%)
TENDERNESS AT TARGET SITE	2 (1.1%)	0 (0.0%)
ERYTHEMA AT REMOTE SITE	3 (1.6%)	0 (0.0%)
PAPULE(S) AT TARGET SITE	3 (1.6%)	0 (0.0%)
BLEEDING AT TARGET SITE	4 (2.2%)	0 (0.0%)
TINGLING AT TARGET SITE	1 (0.5%)	2 (1.1%)
INFECTION AT TARGET SITE	2 (1.1%)	0 (0.0%)

Local skin reactions were collected independently of the adverse event "application site reaction" in an effort to provide a better picture of the specific types of local reactions that might be seen. The prevalence and severity of local skin reactions that occurred during controlled studies are shown in the following table.

Most Intense Local Skin Reactions in the Treatment Area as Assessed by the Investigator (Percentage of Patients)
5X/Week Application

	Mild/Moderate		Severe	
	Aldara Cream n=184	Vehicle n=178	Aldara Cream n=184	Vehicle n=178
Edema	71%	36%	7%	0%
Erosion	54%	14%	13%	0%
Erythema	69%	95%	31%	2%
Flaking/Scaling	87%	76%	4%	0%
Induration	78%	53%	6%	0%
Scabbing/Crusting	64%	34%	19%	0%
Ulceration	34%	3%	6%	0%
Vesicles	29%	2%	2%	0%

THE ADVERSE REACTIONS THAT MOST FREQUENTLY RESULTED IN CLINICAL INTERVENTION (E.G., REST PERIODS, WITHDRAWAL FROM STUDY) WERE LOCAL SKIN AND APPLICATION SITE REACTIONS; 10% (19/185) OF PATIENTS RECEIVED REST PERIODS. THE AVERAGE NUMBER OF DOSES NOT RECEIVED PER PATIENT DUE TO REST PERIODS WAS 7 DOSES WITH A RANGE OF 2 TO 22 DOSES; 79% OF PATIENTS (15/19) RESUMED THERAPY AFTER A REST PERIOD. OVERALL, IN THE CLINICAL STUDIES, 2% (4/185) OF PATIENTS DISCONTINUED FOR LOCAL SKIN/APPLICATION SITE REACTIONS.

In the sBCC studies, 17 of 1266 (1.3%) imiquimod-treated patients developed treatment site infections that required a rest period off Aldara Cream and were treated with antibiotics.

External Genital Warts

In controlled clinical trials for genital warts, the most frequently reported adverse reactions were local skin and application site reactions.
These reactions were usually mild to moderate in intensity; however, severe reactions were reported with 3X/week application. **These reactions were more frequent and more intense with daily application than with 3X/week application.** Some patients also reported systemic reactions. Overall, in the 3X/week application clinical studies, 1.2% (4/327) of the patients discontinued due to local skin/application site reactions. The incidence and severity of local skin reactions during controlled clinical trials are shown in the following table.

Wart Site Reaction as Assessed by Investigator (Percentage of Patients)
3X/Week Application

	Mild/Moderate/Severe				Severe			
	Females		Males		Females		Males	
	Aldara Cream n=114	Vehicle n=99	Aldara Cream n=156	Vehicle n=157	Aldara Cream n=114	Vehicle n=99	Aldara Cream n=156	Vehicle n=157
Erythema	74 (65%)	21 (21%)	90 (58%)	34 (22%)	4 (4%)	0 (0%)	6 (4%)	0 (0%)
Erosion	35 (31%)	8 (8%)	47 (30%)	10 (6%)	1 (1%)	0 (0%)	2 (1%)	0 (0%)
Excoriation/ Flaking	21 (18%)	8 (8%)	40 (26%)	12 (8%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Edema	20 (18%)	5 (5%)	19 (12%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Induration	6 (5%)	2 (2%)	11 (7%)	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ulceration	9 (8%)	1 (1%)	7 (4%)	1 (1%)	3 (3%)	0 (0%)	0 (0%)	0 (0%)
Scabbing	4 (4%)	0 (0%)	20 (13%)	4 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Vesicles	3 (3%)	0 (0%)	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Remote site skin reactions were also reported in female and male patients treated 3X/week with Aldara Cream. The severe remote site skin reactions reported for females were erythema (3%), ulceration (2%), and edema (1%); and for males, erosion (2%), and erythema, edema, induration, and excoriation/flaking (each 1%).

ADVERSE EVENTS JUDGED TO BE PROBABLY OR POSSIBLY RELATED TO ALDARA CREAM REPORTED BY MORE THAN 5% OF PATIENTS ARE LISTED BELOW; ALSO INCLUDED ARE SORENESS, INFLUENZA-LIKE SYMPTOMS AND MYALGIA.

3X/Week Application

	Females		Males	
	Aldara Cream n=117	Vehicle n=103	Aldara Cream n=156	Vehicle n=158
Application Site Disorders:				
Application Site Reactions				
Wart Site:				
Itching	32%	20%	22%	10%
Burning	26%	12%	9%	5%
Pain	8%	2%	2%	1%
Soreness	3%	0%	0%	1%
Fungal Infection*	11%	3%	2%	1%
Systemic Reactions:				
Headache	4%	3%	5%	2%
Influenza-like symptoms	3%	2%	1%	0%
Myalgia	1%	0%	1%	1%

* Incidences reported without regard to causality with Aldara Cream.

Adverse events judged to be possibly or probably related to Aldara Cream and reported by more than 1% of patients included: **Application Site Disorders: Wart Site Reactions** (burning, hypopigmentation, irritation, itching, pain, rash, sensitivity, soreness, stinging, tenderness); **Remote Site Reactions** (bleeding, burning, itching, pain, tenderness, tinea cruris); **Body as a Whole:** fatigue,

fever, influenza-like symptoms; **Central and Peripheral Nervous System Disorders:** headache; **Gastro-Intestinal System Disorders:** diarrhea; **Musculo-Skeletal System Disorders:** myalgia.

POSTMARKETING ADVERSE EVENTS

The following adverse reactions have been identified during post-approval use of Aldara Cream. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: angioedema. **Cardiovascular:** capillary leak syndrome, cardiac failure, cardiomyopathy, pulmonary edema, arrhythmias (tachycardia, atrial fibrillation, palpitations), chest pain, ischemia, myocardial infarction, syncope. **Endocrine:** thyroiditis. **Hematological:** decreases in red cell, white cell and platelet counts. **Hepatic:** abnormal liver function. **Neuropsychiatric:** agitation, cerebrovascular accident, convulsions, depression, insomnia, multiple sclerosis aggravation, paresis, suicide. **Respiratory:** dyspnea. **Urinary System Disorders**: proteinuria. **Skin and Appendages**: exfoliative dermatitis.

OVERDOSAGE

Persistent topical overdosing of Aldara Cream could result in an increased incidence of severe local skin reactions and may increase the risk for systemic reactions. The most clinically serious adverse event reported following multiple oral imiquimod doses of >200 mg (equivalent to imiquimod content of >16 packets) was hypotension, which resolved following oral or intravenous fluid administration.

DOSAGE AND ADMINISTRATION

The application frequency for Aldara Cream is different for each indication.

Actinic Keratosis

Aldara Cream is to be applied 2 times per week for 16 weeks to a defined treatment area on the face or scalp (but not both concurrently). The treatment area should be one contiguous area of approximately 25 cm^2 (e.g., 5 cm x 5 cm). Imiquimod cream should be applied to the entire treatment area (e.g., the forehead, scalp, or one cheek).

Aldara Cream is packaged in single-use packets, with 12 packets supplied per box. Patients should be prescribed no more than 3 boxes (36 packets) for the 16 week treatment period. Unused packets should be discarded. Partially-used packets should be discarded and not reused. Before applying the cream, the patient should wash the treatment area with mild soap and water and allow the area to dry thoroughly (at least 10 minutes). The patient should apply no more than one packet of Aldara Cream to the contiguous treatment area at each application. **Aldara Cream is applied prior to normal sleeping hours, and left on the skin for approximately 8 hours, after which time the cream should be removed by washing the area with mild soap and water.** The cream should be rubbed into the

treatment area until the cream is no longer visible. Contact with the eyes, lips and nostrils should be avoided. Examples of two times per week application schedules are Monday and Thursday, or Tuesday and Friday prior to sleeping hours. **Aldara Cream treatment should continue for the full 16 weeks. However, the treatment period should not be extended beyond 16 weeks due to missed doses or rest periods.** Local skin reactions in the treatment area are common. Patients should contact their physician if they experience any sign or symptom in the treatment area that restricts or prohibits their daily activity or makes continued application of the cream difficult. A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of Aldara Cream therapy. Handwashing before and after cream application is recommended.

Lesions that do not respond to therapy should be carefully re-evaluated and management reconsidered.

Superficial Basal Cell Carcinoma

Aldara Cream is to be applied 5 times per week for 6 weeks to a biopsy-confirmed superficial basal cell carcinoma. The target tumor should have a maximum diameter of no more than 2 cm and be located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet). The treatment area should include a 1 cm margin of skin around the tumor.

Target Tumor Diameter	Size of Cream Droplet to be Used (diameter)	Approximate Amount of Cream to be Used
0.5 to < 1.0 cm	4 mm	10 mg
≥ 1.0 to < 1.5 cm	5 mm	25 mg
≥ 1.5 to 2.0 cm	7 mm	40 mg

ALDARA CREAM IS PACKAGED IN SINGLE-USE PACKETS, WITH 12 PACKETS SUPPLIED PER BOX. PATIENTS SHOULD BE PRESCRIBED NO MORE THAN 3 BOXES (36 PACKETS) FOR THE 6 WEEK TREATMENT PERIOD. UNUSED PACKETS SHOULD BE DISCARDED. PARTIALLY-USED PACKETS SHOULD BE DISCARDED AND NOT REUSED.

ALDARA CREAM IS TO BE APPLIED 5 TIMES PER WEEK, PRIOR TO NORMAL SLEEPING HOURS, AND LEFT ON THE SKIN FOR APPROXIMATELY 8 HOURS. BEFORE APPLYING THE CREAM, THE PATIENT SHOULD WASH THE TREATMENT AREA WITH MILD SOAP AND WATER AND ALLOW THE AREA TO DRY THOROUGHLY. SUFFICIENT CREAM SHOULD BE APPLIED TO COVER THE TREATMENT AREA, INCLUDING ONE CENTIMETER OF SKIN SURROUNDING THE TUMOR. THE CREAM SHOULD BE RUBBED INTO THE TREATMENT AREA UNTIL THE CREAM IS NO LONGER VISIBLE. EYE CONTACT SHOULD BE AVOIDED. FOLLOWING THE TREATMENT PERIOD, CREAM SHOULD BE REMOVED BY WASHING THE AREA WITH MILD SOAP AND WATER. AN EXAMPLE OF A 5 TIMES PER WEEK APPLICATION SCHEDULE IS TO APPLY ALDARA CREAM, ONCE PER DAY, MONDAY THROUGH FRIDAY, PRIOR TO SLEEPING HOURS. **ALDARA CREAM TREATMENT SHOULD CONTINUE FOR 6 WEEKS.** LOCAL SKIN REACTIONS IN THE TREATMENT AREA ARE COMMON. PATIENTS SHOULD CONTACT THEIR PHYSICIAN IF THEY EXPERIENCE ANY SIGN OR SYMPTOM IN THE TREATMENT AREA THAT RESTRICTS OR PROHIBITS THEIR DAILY ACTIVITY OR MAKES CONTINUED APPLICATION OF THE CREAM DIFFICULT. A REST PERIOD OF SEVERAL DAYS MAY BE TAKEN IF REQUIRED BY THE PATIENT'S DISCOMFORT OR SEVERITY OF THE LOCAL SKIN REACTION. THE TECHNIQUE FOR PROPER DOSE ADMINISTRATION SHOULD BE DEMONSTRATED BY THE PRESCRIBER TO MAXIMIZE THE BENEFIT OF ALDARA CREAM THERAPY. HANDWASHING BEFORE AND AFTER CREAM APPLICATION IS RECOMMENDED.

Early clinical clearance cannot be adequately assessed until resolution of local skin reactions. It is appropriate to have the first follow-up visit at approximately 12 weeks post-treatment to assess the treatment site for clinical clearance. Local skin reactions or other findings (e.g. infection) may require

that a patient be seen sooner than the 12 week post-treatment visit. If there is clinical evidence of persistent tumor at the 12 week post-treatment assessment, a biopsy or other alternative intervention should be considered; the safety and efficacy of a repeat course of Aldara Cream treatment have not been established. If any suspicious lesion arises in the treatment area at any time after 12 weeks, the patient should seek a medical evaluation. See table of Estimated Clinical Clearance Rates for Superficial Basal Cell Carcinoma in the CLINICAL STUDIES section.

External Genital Warts

Aldara Cream is to be applied 3 times per week, prior to normal sleeping hours, and left on the skin for 6-10 hours. Patients should be instructed to apply Aldara Cream to external genital/perianal warts. A thin layer is applied to the wart area and rubbed in until the cream is no longer visible. The application site is not to be occluded. Following the treatment period cream should be removed by washing the treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday; or Tuesday, Thursday, Saturday application prior to sleeping hours. Aldara Cream treatment should continue until there is total clearance of the genital/perianal warts or for a maximum of 16 weeks. Local skin reactions (erythema) at the treatment site are common. A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. Treatment may resume once the reaction subsides. Non-occlusive dressings such as cotton gauze or cotton underwear may be used in the management of skin reactions. The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of Aldara Cream therapy. Handwashing before and after cream application is recommended. Aldara Cream is packaged in single-use packets which contain sufficient cream to cover a wart area of up to 20 cm^2; use of excessive amounts of cream should be avoided.

HOW SUPPLIED

Aldara (imiquimod) Cream, 5%, is supplied in single-use packets which contain 250 mg of the cream. Available as: box of 12 packets NDC 0089-0610-12.

Store below 25°C (77°F).
Avoid freezing.

Keep out of reach of children.

Rx only

August 9, 2005

Patient Information
ALDARA [al dar' a] Cream, 5%
(Imiquimod)

Read the Patient Information that comes with Aldara Cream before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or treatment. If you do not understand the information, or have any questions about Aldara Cream, talk with your healthcare provider or pharmacist.

What is Aldara Cream?
Aldara Cream is a skin use only (topical) medicine used to treat:

- external genital and perianal warts in people 12 years and older
- actinic keratosis in adults with normal immune systems. Actinic keratosis is caused by too much sun exposure.
- superficial basal cell carcinoma in adults with normal immune systems when surgical methods are less appropriate. This skin cancer needs to be diagnosed by your healthcare provider.

Aldara Cream is used in different ways for the three different skin conditions it is used to treat. It is very important that you follow the instructions for your skin condition. Talk to your healthcare provider if you have questions.

Aldara Cream does not work for everyone. Aldara Cream will not cure your genital or perianal warts. New warts may develop during treatment with Aldara Cream. It is not known if Aldara Cream can stop you from spreading genital or perianal warts to other people. For your own health and the health of others, it is important to practice safer sex. Talk to your healthcare provider about safer sex practices.

Who should not use Aldara Cream?

- Aldara Cream has not been studied in children under 12 years old for external genital and perianal warts.
- Aldara Cream has not been studied in children under 18 years old for actinic keratosis or superficial basal cell caricnoma. Children usually do not get actinic keratoses or basal cell carcinoma.

Before using ALDARA Cream, tell your healthcare provider

- **about all your medical conditions, including if you:**
  - **are pregnant or planning to become pregnant.** It is not known if Aldara Cream can harm your unborn baby.
  - **are breastfeeding.** It is not known if Aldara Cream passes into your milk and if it can harm your baby.
- **about all the medicines you take including prescription and non-prescription medicines, vitamins and herbal supplements.** Especially tell your healthcare provider if you have had other treatments for genital or perianal warts, or actinic keratosis, or superficial basal cell carcinoma. Aldara Cream should not be used until your skin has healed from other treatments.

How should I use Aldara Cream?

- Use Aldara Cream exactly as prescribed by your healthcare provider. **Aldara Cream is for skin use only. Do not take by mouth or use in or near your eyes, lips or nostrils.** Do not use Aldara Cream unless your healthcare provider has taught you the right way to use it. Talk to your healthcare provider if you have any questions.

- Aldara Cream is used for several skin conditions. **Use Aldara cream only on the area of your body to be treated.** Your healthcare provider will tell you where to apply Aldara cream and how often and for how long to apply it for your condition. Do not use Aldara Cream longer than prescribed. Using too much Aldara Cream, or using it too often, or for too long can increase your chances for having a severe skin reaction or other side effect. Talk to your healthcare provider if Aldara Cream does not work for you.

1. **For external genital and perianal warts** Aldara Cream is usually used once a day for 3 days a week:
   - Monday, Wednesday and Friday, or
   - Tuesday, Thursday and Saturday

For these conditions, Aldara Cream is usually left on the skin for 6 to 10 hours. Treatment should continue until the warts are completely gone, or up to 16 weeks.

2. **For actinic keratosis** Aldara Cream is usually used once a day for 2 days a week, 3 to 4 days apart, such as:
   - Monday and Thursday, or
   - Tuesday and Friday

For this condition, Aldara Cream is usually left on the skin for about 8 hours. Treatment should continue for the full 16 weeks even if all actinic keratoses appear to be gone, unless you are told otherwise by your healthcare provider. The area you treat with Aldara Cream should be no larger than approximately the size of your forehead or one cheek (for example 2 inches by 2 inches), unless otherwise directed by your healthcare provider.

3. **For superficial basal cell carcinoma** Aldara Cream is usually used once a day for 5 days a week:
   - Monday, Tuesday, Wednesday, Thursday and Friday

For this condition, Aldara Cream is usually left on the skin for about 8 hours. Your healthcare provider will show you how much Aldara Cream to apply to your superficial basal cell carcinoma. You should also apply Aldara Cream to a small area of skin all around the superficial basal cell carcinoma. This small area of skin should be about the size of your fingertip. Treatment should continue for the full 6 weeks, even if the superficial basal cell carcinoma appears to be gone, unless you are told otherwise by your healthcare provider.

Applying Aldara Cream

Aldara Cream should be applied just before your bedtime.

- Wash the area to be treated with mild soap and water. Allow the area to dry.
  - Uncircumcised males treating warts under their penis foreskin must pull their foreskin back and clean before treatment, and clean daily during the weeks of treatment.

- Wash your hands
- Open a new packet of Aldara Cream just before use
- Apply a thin layer of Aldara Cream **only** to the affected area or areas to be treated. Do not use more Aldara cream than is needed to cover the treatment area.
- Rub the cream in all the way to the affected area or areas.
  - Do not get Aldara Cream in your eyes.
  - Do not get Aldara Cream in the anus when applying to perianal warts.
  - Female patients treating genital warts must be careful when applying Aldara Cream around the vaginal opening. Female patients should take special care if applying the cream at the opening of the vagina because local skin reactions on the delicate moist surfaces can cause pain or swelling, and may cause problems passing urine. Do not put Aldara Cream in your vagina or on the skin around the genital wart.
- Do not cover the treated area with an airtight bandage. Cotton gauze dressings can be used. Cotton underwear can be worn after applying Aldara Cream to the genital or perianal area.
- Safely throw away the open packet of Aldara Cream so that children and pets cannot get it. The open packet should be thrown away even if all the Aldara Cream was not completely used.
- After applying Aldara Cream, **wash your hands well.**
- Leave the cream on the affected area or areas for the time prescribed by your healthcare provider. The length of time that Aldara Cream is left on the skin is not the same for the different skin conditions that Aldara Cream is used to treat. Do not bathe or get the treated area wet before the right time has passed. Do not leave Aldara Cream on your skin longer than prescribed.
- After the right amount of time has passed, wash the treated area or areas with mild soap and water.
- If you forget to apply Aldara Cream, apply the missed dose of cream as soon as you remember and then continue on your regular schedule.
- If you get Aldara Cream in your mouth or in your eyes rinse well with water right away.

What should I avoid while using Aldara Cream?

- Do not cover the treated site with bandages or other closed dressings. Cotton gauze dressings are okay to use, if needed. Cotton underwear can be worn after treating the genital or perianal area.
- Do not apply Aldara Cream in or near the eyes, lips or nostrils, or in the vagina or anus.
- Do not use sunlamps or tanning beds, and avoid sunlight as much as possible during treatment with Aldara Cream. Use sunscreen and wear protective clothing if you go outside during daylight.
- Do not have sexual contact including genital, anal, or oral sex when Aldara Cream is on your genital or perianal skin. Aldara Cream may weaken condoms and vaginal diaphragms. This means they may not work as well to prevent pregnancy. For your own health and the health of others, it is important to practice safer sex. Talk to your healthcare provider about safer sex practices.

What are the possible side effects of Aldara Cream?

The most common side effects with Aldara Cream are skin reactions at the treatment site including:

- redness
- swelling
- a sore, blister, or ulcer
- skin that becomes hard or thickened

- skin peeling
- scabbing and crusting
- itching
- burning
- changes in skin color that do not always go away

Actinic Keratosis
During treatment and until the skin has healed, your skin in the treatment area is likely to appear noticeably different from normal skin. Side effects, such as redness, scabbing, itching and burning are common at the site where Aldara Cream is applied, and sometimes the side effects go outside of the area where Aldara Cream was applied. Swelling, small open sores and drainage may also be experienced with use of Aldara Cream. You may also experience itching and/or burning. Actinic keratoses that were not seen before may appear during treatment and may later go away. If you have questions regarding treatment or skin reactions, please talk with your healthcare provider.

Superficial Basal Cell Carcinoma
During treatment and until the skin has healed, your skin in the treatment area is likely to appear noticeably different from normal skin. Side effects, such as redness, swelling and a sore are common at the site where Aldara Cream is applied. You may also experience itching or burning. Your healthcare provider will need to check the area that was treated after your treatment is finished to make sure that the skin cancer is gone. Superficial basal cell carcinoma can come back. The chances of it coming back are higher as time passes. **It is very important to have regular follow-up visits with your healthcare provider to check the area to make sure your skin cancer has not come back. Ask your healthcare provider how often you should have your skin checked.** Talk with your healthcare provider if you have questions about your treatment or skin reactions.

External Genital and Perianal Warts
Patients should be aware that new warts may develop during treatment, as Aldara Cream is not a cure. Many people see reddening or swelling on or around the application site during the course of treatment. If you have questions regarding treatment or local skin reactions, please talk with your healthcare provider.

You have a higher chance for severe skin reactions if you use too much Aldara Cream or use it the wrong way. **Stop Aldara Cream right away and call your healthcare provider if you get any skin reactions that affect your daily activities, or that do not go away.** Sometimes, Aldara Cream must be stopped for a while to allow your skin to heal. Talk to your healthcare provider if you have questions about your treatment or skin reactions.

Other side effects of Aldara Cream include headache, back pain, muscle aches, tiredness, flu-like symptoms, swollen lymph nodes, diarrhea, and fungal infections.

If the reactions seem excessive, if either skin breaks down or sores develop during the first week of treatment, if flu-like symptoms develop or if you begin to not feel well at anytime, contact your healthcare provider.

These are not all the side effects of Aldara Cream. For more information, ask your healthcare provider or pharmacist.

How do I store Aldara Cream?
- Store Aldara Cream below 77° F (25° C). Do not freeze.
- Safely throw away Aldara Cream that is out of date or that you do not need.
- **Keep Aldara Cream and all medicines out of the reach of children.**

General information about Aldara Cream
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Aldara Cream for a condition for which it was not prescribed. Do not give Aldara Cream to other people, even if they have the same symptoms you have.

This leaflet summarizes the most important information about Aldara Cream. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Aldara Cream that is written for the healthcare provider. If you have other questions about Aldara Cream, call 1-888-2-ALDARA. Visit our website at http://www.Aldara.com.

What are the ingredients in Aldara Cream?
Active Ingredient: imiquimod
Inactive ingredients: isostearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben.

Rx Only

3M
3M Pharmaceuticals
275-3W-01 3M Center
St. Paul, MN 55144-1000

August 9, 2005

EXHIBIT 41

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-723/S-001

3M Pharmaceuticals
Attention: Mark A. Morken, R.Ph
Senior Regulatory Associate
3M Center, Building 270-3A-08
St. Paul, Minnesota 55144-1000

Dear Mr. Morken:

Please refer to your supplemental new drug application dated April 4, 1997, received April 7, 1997 submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Aldara (imiquimod) Cream, 5%.

We acknowledge receipt of your submissions dated April 28, 1997 and dated August 23, 2001.

This supplemental new drug applications provides for the revision of the Pharmacodynamics subsection under the Clinical Pharmacology section.

We have completed the review of this supplemental applications as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed agreed upon labeling (text for the package insert).

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format-NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-723/S-001." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Millie Wright, Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonathan Wilkin
12/8/01 04:51:26 PM

EXHIBIT 42

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-535

ADMINISTRATIVE DOCUMENTS

Division Director's Summary Review of NDA 21-535

Sponsor:	Galderma Laboratories, L.P. 14501 North Freeway Forth Worth, TX 76177 USA
Generic name:	Clobetasol Propionate
Trade name:	Clobex
Chemical name:	Clobetasol Propionate
Pharmacologic Category:	Anti-inflammatory
Indication:	Moderate to Severe Plaque Psoriasis and — Dermatitis
Dosage Forms (s):	Lotion.
Route (s) of Administration:	Topical

I. Reviewing Disciplines' Conclusions:

A. Chemistry Review dated 6/27/03:

"After evaluation for GMP compliance, all three manufacturing and testing facilities were found to be acceptable. Clobetasol propionate, is a well-established chemical whose structure has been fully elucidated. It is characterized through the USP monograph, and listed in USAN and in the Merck Index (additional data). The DMF of the main drug substance supplier has been updated, reviewed and found to be adequate. The NDA submission and its amendments (responses to information request letters) provide adequate information on the chemistry, manufacturing and controls for the production of Clobex (clobetasol propionate) Lotion, 0.05%.

"From a chemistry, manufacturing and controls standpoint (sic: it) is approvable pending action by the applicant to withdraw [redacted] as an alternate [redacted] supplier."

The applicant withdrew the reference to DMF [redacted] pertaining to [redacted] in correspondence dated July 1, 2003, resolving the sole remaining CMC approvability issue.

B. Pharmacology/Toxicology Review dated 3/20/03:

"The nonclinical studies conducted by the sponsor confirm that clobetasol propionate has teratogenic potential. A teratogencity study in rats using the dermal route resulted in dose related maternal toxicity and fetal effects from 0.05 to 0.5 mg/kg/day of Clobetasol propionate. These doses are approximately 0.14 to 1.4 times, respectively, the human topical dose of Clobetasol Propionate Lotion, 0.05%. Abnormalities seen included low fetal weights, umbilical herniation, cleft palate, reduced skeletal ossification other skeletal abnormalities. Other nonclinical findings suggest that the lotion did not cause skin sensitization and was not irritating to the skin or eye."

No new pharmacology information was submitted by the sponsor, since this was a 505(b)(2).

"No new safety issues relevant to clinical use have been identified in the studies conducted by the sponsor. The teratogenic potential of clobetasol propionate is addressed in the label.

"The application is approvable from a pharm/tox perspective provided the sponsor agrees to conduct the recommended phase 4 nonclinical studies.

"It is recommended that the sponsor be asked to agree to conduct a dermal carcinogenicity study and an evaluation of the photocarcinogenic potential of the drug product as phase 4 commitments."

C. Clinical Pharmacology & Biopharmaceutics Review dated 7/1/03:

"From a Biopharmaceutics perspective the firm has provided evidence of systemic availability for the test Clobex Propionate Lotion and reference Temovate E Emollient cream formulations. Based on the results of the 3 HPA axis trials, use of CP Lotion is clearly associated with a high incidence of HPA suppression compared to the Temovate E Emollient cream. Thus, from a clinical pharmacology perspective, there is a reasonable concern about the safety of this product in uncontrolled administration. While the bioavailability of clobetasol has been determined via indirect methods (i.e., HPA axis testing), the safety issues raised by the increased bioavailability relative to the reference product raises a significant concern."

The basis for the "significant concern" is that this product is "clearly associated with a high incidence of HPA suppression compared to the Temovate E Emollient Cream." This "significant concern" of "the safety issues raised by the increased bioavailability" will be addressed in the discussion of the Clinical Review (below).

D. Biostatistics Review dated 5/7/03:

The ITT analysis with LOCF for missing data demonstrated that Clobex Lotion is superior to its vehicle for all primary endpoints in Studies 9707 (psoriasis), 18001 (atopic dermatitis), and 2651 (psoriasis). Study 2651 was regarded as supportive and Studies 9707, and 18001 as pivotal, by both the Biostatistics and Clinical disciplines.

Formal statistics for the HPA axis suppression studies were not described in the Biostatistics Review, and the small numbers of subjects tested for HPA axis suppression do not readily invite formal statistical analysis.

"From statistical point of view, the safety profile of Clobex Lotion is comparable to those Temovate E Cream (or Dermoval Cream for Study 2651) and Lotion vehicle in terms of the incidence of adverse events and cutaneous skin reaction."

The essential findings in the Biostatistics Review are the same as found in the Clinical Review, where they will be discussed (below) in the regulatory context of a 505(b)(2) submission.

E. Clinical Review dated (by Team Leader) 06/12/03:
The Medical Officer and Team Leader describe multiple conclusions:

1. "There is no doubt that clobetasol propionate as chemical moiety in a topical formulation is a super high potency anti-inflammatory drug product capable of treating corticosteroid responsive dermatoses. This was demonstrated in the two pivotal trials. Clobetasol propionate lotion (CP Lotion) was statistically superior to its lotion vehicle ($p \leq 0.001$)."
2. "In terms of efficacy, the Division allows for a 10% margin of non-inferiority compared to the RLD. In both the psoriasis trial and the atopic dermatitis trial, clobetasol propionate lotion had a margin of greater than 10% inferiority as compared to Temovate E (18.9% and 12.0%, respectively). In the atopic dermatitis trial, where the margin was closer to 10%, CP lotion failed in 3 of the 4 secondary variables, erythema, oozing/crusting, and pruritus."
3. "In terms of safety, while the cutaneous safety profiles of the two drug products are similar, the systemic safety profile, which in my opinion, is the major issue, of clobetasol propionate lotion is much worse than that of Temovate E Emollient Cream. The endpoint examined for systemic safety was the potential to suppress the HPA axis. CP Lotion

— However, this drug caused HPA axis suppression at some point during treatment of psoriasis in 80% of patients as compared to 33% in patients treated with Temovate E. Furthermore, at the end of the study 40% of patients had HPA axis suppression compared to 0% treated with Temovate E. This study further demonstrates that the potential for HPA axis suppression by clobetasol propionate lotion may be underestimated as the adrenal glands of the patients were constantly being stimulated (almost q week during the study) and suppression still occurred at the endpoint (4 weeks) for patients on CP Lotion but not in patients on Temovate E. Lastly, although the BSA treated in this study was higher than that approved for Temovate E, one has to assume that the comparison of the proportion of suppression between the two drugs, although lower, would be the same."
4. "The greater ability of CP lotion to cause HPA axis suppression is substantiated in the atopic dermatitis studies, of which the adolescent study is demonstrative. In this study 64.3% of patients experienced HPA axis suppression on CP lotion compared to 20% of those who used Temovate E."
5. "The time to recovery from HPA axis suppression was not clear for all the patients who had follow-up. A greater number did not recover in the time tested who were treated with clobetasol propionate lotion as compared to Temovate E Emollient Cream."
6. "The question to be answered ultimately in review of this application, when considering the risk/benefit analysis of clobetasol propionate lotion, is, ' Does clobetasol propionate lotion offer any advantage in the interest of the public health over the clobetasol propionate formulation that is currently marketed?' In my opinion, the answer is, 'No, it does not offer any advantage.' It is not efficacious as Temovate E Emollient Cream in treating corticosteroid responsive dermatoses while at the same time presents an

increased risk to the safety of the public health by having a poorer systemic safety profile as compared to Temovate E Emollient Cream."

The Medical Officer and Team Leader recommend "that the action taken for the new drug application of clobetasol propionate lotion be that of non-approvable."

I agree with some of their conclusions and not with others:

1. I agree that Clobex Lotion is superior to its lotion vehicle in effectiveness.
2. I agree that there was insufficient evidence to conclude that Clobex Lotion is non-inferior to the reference listed drug product, Temovate E Emollient Cream; however, I disagree that this would be an essential requirement for approval (see below).
3. I agree that the local safety profile is similar for Clobex Lotion and Temovate E Emollient Cream.
4. I disagree that the systemic safety profile of Clobex Lotion (which is regarded as " the major issue" in the Clinical Review) is "much worse than that of Temovate E Emollient Cream" (see below).
5. I agree that 9 of 14 adolescent patients with atopic dermatitis had evidence of HPA axis suppression associated with Clobex Lotion. This product will be indicated for adults only.
6. I disagree that "the question to be answered ultimately in review of this application, when considering the risk/benefit analysis of clobestasol propionate lotion, is, 'Does clobetasol propionate lotion offer any advantage in the interest of the public health over the clobetasol propionate formulation that is currently marketed'?" Pages 27-29 of Reinventing Drug & Medical Device Regulations, National Performance Review (April 1995) address the " Effectiveness of Drugs and Devices." The key passage states: " For the majority of new drugs and Class III devices, i.e., new products intended to treat less serious illness or provide relief from symptoms, a showing of effectiveness is usually based on a clinical trial comparing the product to a placebo. Such a showing does not involve a comparison to any other product."

I will address the remaining disagreements, which are 1) whether there is a requirement for demonstrating non-inferiority (in efficacy) to the reference listed drug product and 2) whether the systemic safety (HPA axis suppression) profile of Clobex Lotion is "much worse" than that of the reference listed drug product in the following analysis of this NDA.

The essential feature of a 505 (b)(2) application is that the applicant may rely on the Agency's finding of efficacy and/or safety from the labeling of a reference listed drug product by sufficiently comparing the bioavailabilities of their test product with the reference listed drug product. For topical products, bioavailability comparisons are generally obtained from clinical trials employing the endpoints of efficacy and safety. For topical corticosteroids there is generally also a comparative HPA axis suppression test (or tests, in the case of different dosing regimens in the same application).

The analysis of a 505 (b)(2) approach begins with the determination of the informational needs for a 505(b)(1) application according to current standards. Often, the reference listed drug product does not have labeling information sufficient for current standards, and the applicant must supply such additional information through studies they have conducted or obtained by right of reference. Also, the applicant may provide adequate information demonstrating efficacy or some aspect of safety that meets the needs for a 505(b)(1) application, such that they need not rely on the Agency's finding

from the labeling of the reference listed product for that particular informational need. Thus, the comparison of bioavailabilities with the reference listed drug product needs only to support the Agency's finding from the labeling of a reference listed drug product of that specific, essential information piece not otherwise provided by the applicant's studies or through right of reference.

Often, topical product NDAs are 505 (b)(2) applications in which the sponsor relies on the Agency's finding of efficacy from the labeling of a reference listed drug product, e.g., when the vehicle is sufficiently different from that of the reference listed drug product owned by a different manufacturer. In such cases, the sponsor must demonstrate non-inferiority to the reference listed drug product and superiority to the new vehicle. Although this has been a common architectural feature of the information structure in many 505 (b)(2) applications, the finding of non-inferiority to the reference listed drug product is not essential, if the applicant provides sufficient information separately to document effectiveness. The comparative bioavailability bridge need only support the Agency's finding from the labeling of the reference listed drug product for which the applicant has not otherwise produced sufficient evidence through studies they have conducted or through right of reference.

This NDA adduces sufficient evidence for efficacy for a 505 (b)(1) application, viz., two adequate and well-controlled studies (9707 and 18001) in which the product is clearly superior to vehicle. Accordingly, there is no need to demonstrate non-inferiority to the referenced listed drug product, since the applicant is not relying on the Agency's finding of efficacy from the labeling of the reference listed drug product. The demonstration of superiority to vehicle in psoriasis and atopic dermatitis in separate studies is sufficient for the corticosteroid – responsive dermatoses indication.

In addition to evidence for efficacy, the analysis of a 505 (b)(2) approach involves the determination of the informational needs for safety for a 505(b)(1) application according to current standards. Evidence for safety is divided into two parts: non-clinical and clinical. The first part, non-clinical, has not been established independently by the applicant in this NDA, and the applicant is relying on the Agency's finding of non-clinical safety from the labeling of the reference listed drug product. Also, the applicant has made specific post-marketing commitments to provide additional non-clinical safety information for informational needs that could be provided post-approval for the same product in a strictly 505 (b)(1) application.

The clinical evidence for safety in this NDA is divided into two parts: local and systemic. Both the Clinical Review and the Biostatistics Review conclude that Clobex Lotion and Temovate E Emollient Cream have similar local safety findings. Both the Clinical Review and the Biostatistics Review conclude that Clobex Lotion was not found to be non-inferior to Temovate E Emollient Cream according to the efficacy endpoints. Accordingly, the logic of 320.24 (b)(4) would indicate that the rate and extent of absorption of the active ingredient in Clobex Lotion at the site of action, viz., locally, would be at most equivalent to, and plausibly somewhat less than, Temovate E Emollient Cream. If Clobex Lotion is at most equivalent to Temovate E Emollient Cream, then it is permissible to rely on the Agency's findings of local safety for the active moiety from the labeling of the reference listed drug product. The additional evidence for local safety from studies 9707, 2651, and 18001 and from the requisite human dermal safety studies,

2129 and 1802, is sufficient to conclude that the local safety information base is adequate and that local safety is acceptable for the intended use of the product.

The clinical evidence for systemic safety for topical (gluco-) corticosteroids is generally derived from HPA axis suppression studies. There are general aspects of such HPA axis suppression studies and utility of outcomes that are independent of this specific NDA that must be considered before addressing the evidence in this NDA. Importantly, the primary clinical utility of HPA axis suppression study outcomes is whether HPA axis may occur at maximal duration, amount per week, and body surface area involved, according to labeled conditions of use. Very precise point estimates of HPA axis suppression "risk" provide minimal additional utility, since there are many variables that determine whether suppression occurs, such as prior corticosteroid use, body surface area of involvement, anatomic region of involved skin, thickness of product application, etc. It is not uncommon for HPA axis suppression studies to show suppression in patients with smaller body surface areas of involvement compared with patients with larger body surface areas of involvement who do not suppress. There is no adequate model based on these variables that can predict who will suppress. Accordingly, it is not possible to incorporate a very precise point estimate from HPA axis suppression studies of new drug products into a heuristic that will allow a clinician to determine which patient is at risk for suppression. At best, HPA axis suppression studies can identify risk at maximal conditions of labeled use as unlikely, possible, or probable.

Because of the multiple degrees of freedom in the topical corticosteroid-induced adrenal suppression model, the ability of comparative adrenal suppression studies to detect true differences in the potential for adrenal suppression between two products depends on the numbers of subjects tested and the degree to which the identifiable variables are controlled. In most comparative adrenal suppression studies the large number of identifiable variables and difficulty in recruiting such patients into the study preclude strong inferences regarding differences in potential for adrenal suppression between two products, especially when numbers of subjects actually tested are small.

This NDA includes studies of HPA axis suppression comparing Clobex Lotion and Temovate E Emollient Cream for both four weeks' duration in adult patients with psoriasis (Study 9708) and two weeks' duration in adult patients with atopic dermatitis (Study 18009). In Study 9708, 8 of 10 patients suppressed with Clobex Lotion and 3 of 10 patients suppressed with Temovate E Emollient Cream. The requisite condition for the Chi-Square Test, a minimum of 5 per cell, is not met, since half of the cells have counts less than 5. Two-sided Fisher's Exact Test computationally gives $p \leq 0.07$; however, for this test the assumption of fixed margins is very restrictive for interpretation of findings. Simply stated, the denominators are too small to provide strong inferences by statistical methods. In Study 18009, 5 of 9 patients suppressed with Clobetasol Lotion and 4 of 9 patients suppressed with Temovate E Emollient Cream. Two-sided Fisher's Exact Test computationally gives a probability of 1.00; however, for this test the assumption of fixed margins is very restrictive for interpretation of findings. The denominators are even smaller than Study 18009. Thus, in adult patients with psoriasis and atopic dermatitis, Clobex Lotion demonstrated rates of HPA axis suppression that were numerically higher than those of Temovate E Emollient Cream, although the small numbers studied do not allow for strong statistical inferences that Clobex Lotion is

"much worse" than Temovate E Emollient Cream in the potential for causing HPA axis suppression.

However, it is fair to state that both Clobex Lotion and Temovate E Emollient Cream present a relatively high risk for HPA axis suppression when used at maximal conditions of labeled use. There are clear statements of such risk in the final draft labeling agreed to by the sponsor, along with limiting the indication to adults only and stating explicitly that "use in patients younger than 18 years of age is not recommended due to numerically high rates of HPA axis suppression."

In sum, I find that adequate evidence has been provided in this NDA to find that this product is safe and effective for its intended use per labeled conditions, including precautionary language regarding the potential for HPA axis suppression. A post-marketing commitment to conduct HPA axis suppression tests without interim adrenal stimulation will provide useful information for product labeling in the future

F. Conclusion

This NDA is sufficient for approval since the sponsor has committed to perform the recommended post-marketing studies, both non-clinical and clinical, and has accepted the final draft labeling proposed to sponsor.

/S/

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonathan Wilkin
7/24/03 03:03:14 PM
MEDICAL OFFICER

EXHIBIT 43

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-535

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-535

Galderma Laboratories, L.P.
Attention: Paul M. Clark
Vice President, Regulatory Affairs
14501 N. Freeway
Fort Worth, TX 76177

Dear Mr. Clark:

Please refer to your new drug application (NDA) dated September 25, 2002, received September 27, 2002, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Clobex (clobetasol propionate) Lotion, 0.05%.

We acknowledge receipt of your submissions dated January 10, January 27, January 28, February 6, February 10, February 19 (2), February 27, April 24, May 9, June 10, July 1, July 3, July 7, and July 22, 2003 (facsimile).

This new drug application provides for the use of Clobex (clobetasol propionate) Lotion, 0.05%, for treatment of corticosteroid responsive dermatoses.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission **"FPL for approved NDA 21-535."** Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated July 22, 2003. These commitments are listed below.

1. The Applicant commits to performing dermal carcinogenicity testing of the drug product.

   Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission: Within 4 months of the date of this letter
Study Start: Within 6 months of the date of the approval of the protocol
Final Report Submission: Within 12 months after the study completion

2. The Applicant commits to a study to evaluate the effects of the drug product on UV-induced skin cancers.

   Commitment Category: NON-CLINICAL TOXICOLOGY

   Protocol Submission: Within 4 months of the date of this letter
   Study Start: Within 6 months of the date of the approval of the protocol
   Final Report Submission: Within 12 months after the study completion

3. The Sponsor commits to performing an HPA axis suppression study in no less than 60 evaluable patients using cosyntropin stimulation testing (conducted as labeled with stimulated serum cortisol levels at 30 minutes with any suppressed patients followed to recovery, stimulation should only be conducted at baseline and at the end of the two or four week treatment period) in adult patients with psoriasis or atopic dermatitis. Clobex Lotion should be applied to lesional skin at the maximum amounts permitted in labeling.

   The minimum number of subjects (separate cohorts for each) committed to are as follows:
   a) no less than 30 evaluable adult patients with psoriasis or atopic dermatitis of no less than 20% BSA after 2 weeks of treatment
   b) no less than 30 evaluable adult patients with psoriasis of no less than 10% BSA after 4 weeks of treatment

   Commitment Category: CLINICAL SAFETY ASSESSMENT
   Protocol Submission: Within 4 months of the date of this letter
   Study Start: Within 6 months of the date of the approval of the protocol
   Final Report Submission: Within 16 months after approval of the protocol

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Melinda Harris, M.S., Regulatory Project Manager, at 301-827-2020.

Sincerely,

{See appended electronic signature page}
Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation & Research

Enclosure (Labeling)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonathan Wilkin
7/24/03 03:15:00 PM

EXHIBIT 44

Center for Drug Evaluation and Research

REPORT TO THE NATION 2005

Improving Public Health Through Human Drugs

Statistics

Drug Safety

Drug Quality

Adverse Events

MedWatch

Withdrawals

New Drugs

New Therapeutic Biologics

Generic Drugs

Over-the-Counter Drugs

International Activities

Communications

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

U.S. Department of
Health and Human Services

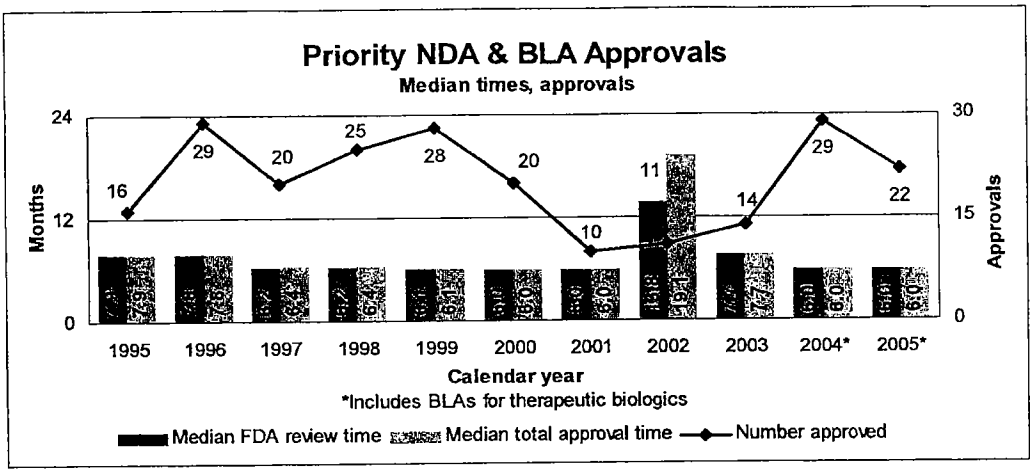
Food and Drug Administration
Center for Drug Evaluation
and Research

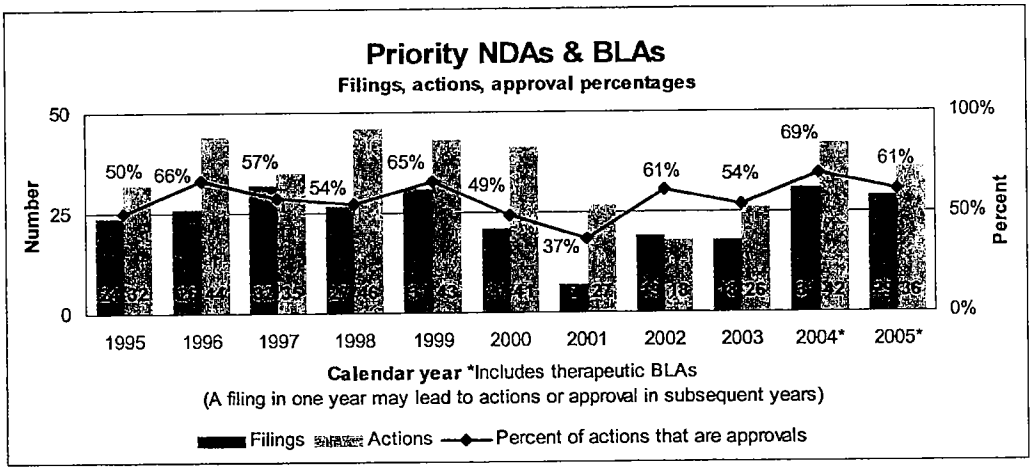
Center for Drug Evaluation and Research ***2005***

Report to the Nation

Improving Public Health Through Human Drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research





Priority new drugs and biologics

- **22 approvals**
  - 20 drugs
  - 2 biologics
- Median review time: 6.0 months
- Median approval time: 6.0 months
- 29 filings
- 36 actions

- **9 orphan approvals**
  - 8 drugs (6 NMEs)
  - 1 new biologic

Notable 2005 New Approvals

Last year's approvals benefited children, people with HIV infection, cancer, diabetes and other disorders.

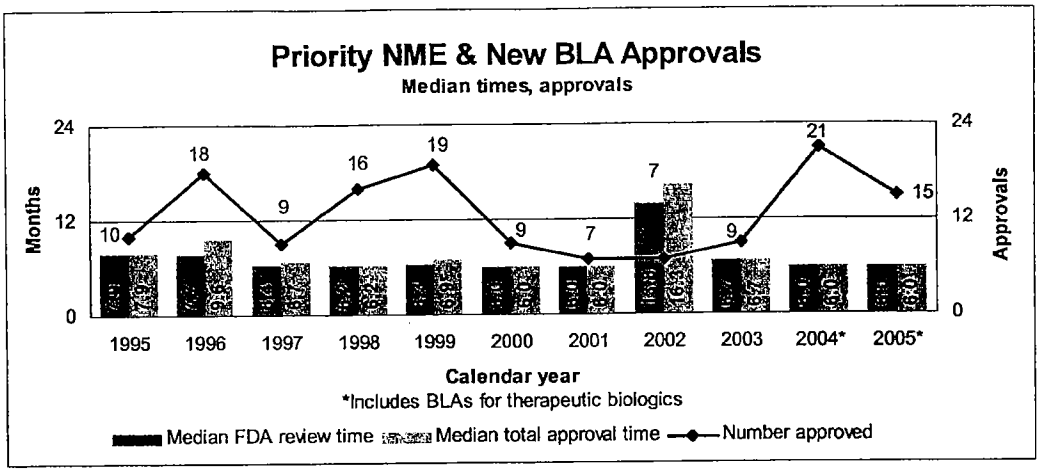
Children

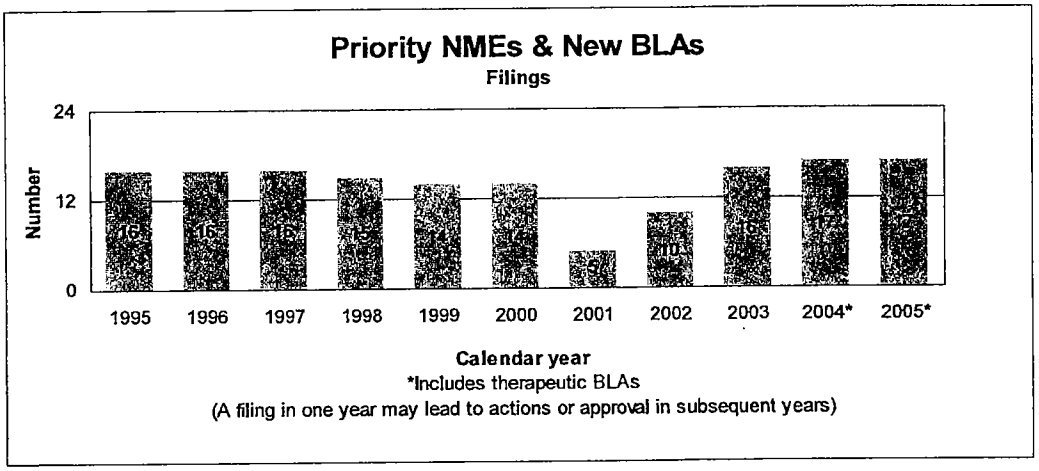
Emtricitabine (Emtriva) is an oral solution of an antiretroviral medicine that can be used in combination with other antiretroviral agents for the treatment of HIV infection in children 3 months old and older. The drug, first approved as a capsule for adults in 2003, is an HIV nucleoside reverse transcriptase inhibitor that helps to block an enzyme needed for HIV to multiply. Related to Best Pharmaceuticals for Children Act. *(priority)*

Mecasermin [rDNA origin] (Increlex) and *Mecasermin rinfabate [rDNA origin] (Iplex)* are for the long-term treatment of children who are very short for their age because their bodies do not make enough insulin-like growth factor-1. Both drugs contain human insulin-like growth factor-1 from genetically engineered bacteria, but mecasermin rinfabate also contains insulin-like growth factor binding protein-3 from genetically engineered bacteria. *(2 NMEs, priorities, orphans)*

Priority new molecular entities and new biologics

- **15 approvals**
- 13 NMEs
- 2 new BLAs
- Median review time: 6.0 months
- Median approval time: 6.0 months
- 17 filings



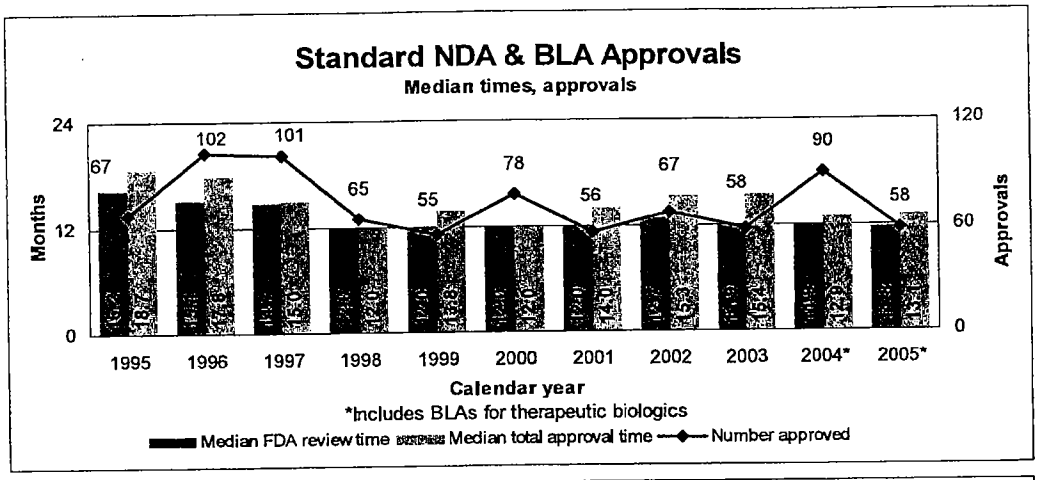


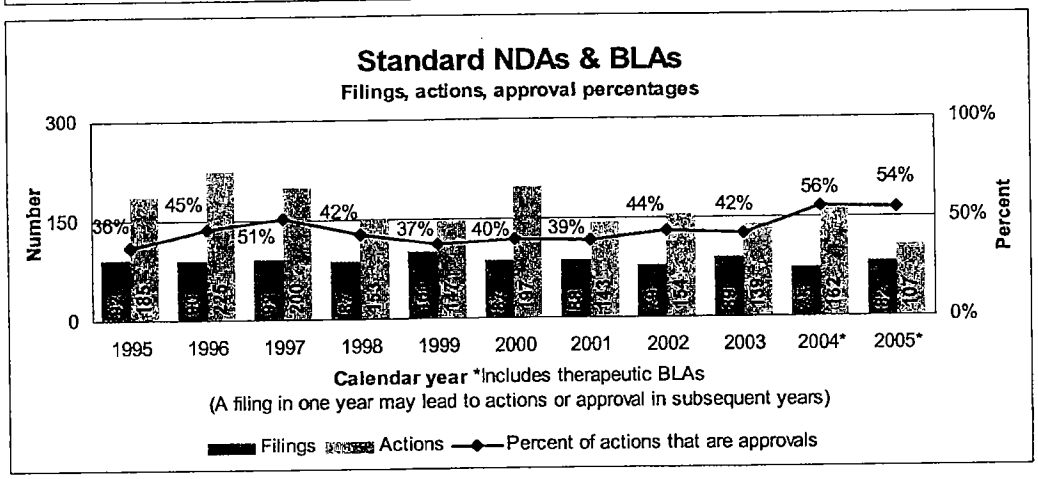
People with HIV infection

Lopinavir/ritonavir (Kaletra) is a new formulation in a tablet form that may be prescribed for once-daily use in combination with other anti-HIV medicines for some patients who have not taken anti-HIV medications in the past. *(priority)*

Tipranavir (Aptivus) is a protease inhibitor taken with 200 mg of ritonavir and two other anti-HIV medicines to treat adults with HIV infection. The drug blocks HIV protease, an enzyme needed for HIV to make more virus. Tipranavir helps reduce the amount of HIV in the blood and keep the immune system healthy so it can help fight infection. *(NME, priority)*

Lamivudine/zidovudine/nevirapine is the first three-drug HIV regimen in one package approved for purchase under the President's Emergency Plan for AIDS Relief (page 51). We gave it "tentative approval" in less than two weeks because patent or exclusivity provisions prevent its sale in the United States. It can also serve as a reference product for generic versions. *(priority)*





Standard drugs and biologics

- **58 approvals**
- 58 drugs
- Median review time: 11.8 months
- Median approval time: 13.1 months
- 82 filings
- 107 actions
- 1 orphan approval

Notable 2005 new drug approvals (continued)

People with cancer

Nelarabine (Arranon) is a chemotherapy drug for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. *(NME, priority, orphan)*

Sorafenib tosylate (Nexavar) is a chemotherapy agent indicated for the treatment of patients with advanced cancer of the kidney cells. *(NME, priority, orphan)*

People with infections

Entecavir (Baraclude), in tablets and oral solution, treats chronic infection with hepatitis B virus in adults who also have active liver damage. Entecavir, a nucleoside analogue, competes with a natural substance needed for viral replication. The tablet form was counted as an NME. We also provided priority approval to a separate application for the oral solution. *(1 NME, both priorities)*